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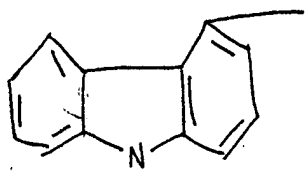
Please search

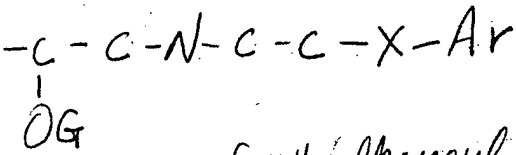
a method of treating congestive heart failure comprising administering a compound that is both a β-adrenoreceptor antagonist

and

an α_1-adrenoreceptor antagonist

as, for example,





G = H, alkanoyl, aroyl

X = a bond, $-CH_2-$, O, S

Ar = phenyl, naphthyl, indanyl or tetrahydronaphthyl

Thanks

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- ___ A.A. Sequence
- ✓ Structure
- ___ Bibliographic

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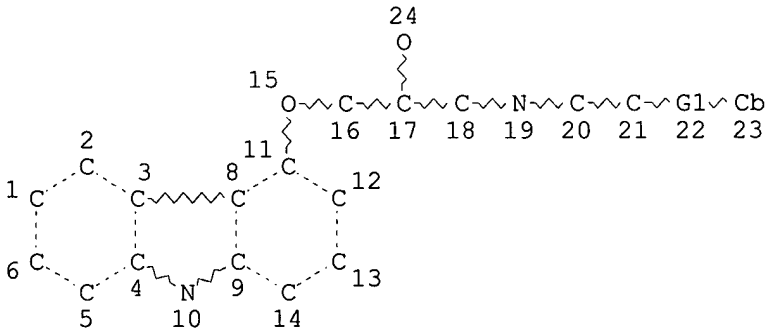


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE
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                OR INFAR?)
L10          58 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND (?ANTAG? OR ?ADRE
                NO? OR RECEP?)

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L10 ANSWER 1 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1998:160108 HCAPLUS
TI .beta.-blockade in heart failure. Basic concepts and clinical results
AU Packer, Milton
CS Division of Circulatory Physiology, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, USA
SO Am. J. Hypertens. (1998), 11(1, Pt. 2), 23S-37S
CODEN: AJHYE6; ISSN: 0895-7061
PB Elsevier Science Inc.
DT Journal; General Review
LA English
AB A review with 98 refs. Both exptl. and clin. observation suggest that activation of the sympathetic nervous system exerts an important deleterious effect in patients with chronic heart failure. The precise mechanisms responsible for this effect have not been defined, but prolonged exposure to norepinephrine is assocd. with a variety of adverse physiol. and biochem./mol. actions. Identification of these deleterious pathways has helped to explain why drugs that block the cardiac effects of norepinephrine (ie, .beta.-blockers) retard remodeling and prolong life in exptl. models of heart failure. .beta.-Blockers have been shown to reduce the mortality of patients after an acute myocardial infarction; this effect appears to be particularly marked in patients with postinfarction heart failure. Results of several trials suggest that long-term treatment with .beta.-blockers can improve symptoms and reduce the frequency of hospitalizations for heart failure. Most recently, carvedilol has been shown to reduce the risk of all-cause mortality by 65% in patients with either an ischemic or nonischemic cardiomyopathy. These findings, taken together, suggest that pharmacol. interference with the sympathetic nervous system can produce important clin. benefits in patients with left ventricular systolic dysfunction.
IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-blocker treatment effects in humans with **heart** failure)

L10 ANSWER 2 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1998:160106 HCAPLUS
DN 128:238867
TI Recent observations with .beta.-**adrenoceptor** blockade. Beneficial effects in hypertension and heart failure
AU Ruffolo, Robert R., Jr.; Feuerstein, Giora Z.; Ohlstein, Eliot H.
CS Division of Pharmacological Sciences, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406-0939, USA
SO Am. J. Hypertens. (1998), 11(1, Pt. 2), 9S-14S
CODEN: AJHYE6; ISSN: 0895-7061
PB Elsevier Science Inc.
DT Journal; General Review
LA English
AB A review with 29 refs. Carvedilol is a third-generation vasodilating .beta.-blocker initially approved for the treatment of hypertension. It lowers systemic arterial blood pressure without causing reflex tachycardia and preserves renal function. More recently, carvedilol has been shown to reduce morbidity and mortality in patients with congestive heart failure. This redn. may occur in part via .beta.-blockade and .alpha.1-**adrenoceptor** blockade, the latter resulting in vasodilation. Importantly, carvedilol and several of its metabolites are potent antioxidants

that may inhibit the oxidn. of norepinephrine and the subsequent formation of toxic intermediates, such as reactive free radicals in the myocardium. As a result, carvedilol inhibits the expression of certain genes involved in myocardial damage, such as intracellular adhesion mol.-1, free-radical-induced activation of transcription factors, and programmed cell death or apoptosis. In this respect, carvedilol represents a new therapy for the treatment of hypertension and congestive heart failure and combines, in one mol., a no. of potentially beneficial properties.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol .beta.-**adrenoceptor** blockade in lab. animals and humans with hypertension and **heart** failure)

L10 ANSWER 3 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1998:154067 HCAPLUS
TI Carvedilol update IV: Prevention of oxidative stress, cardiac remodeling and progression of congestive heart failure
AU Feuerstein, Giora Z.; Shusterman, Neil H.; Ruffolo, Robert R., Jr.
CS Spain
SO Drugs Today (1998), 34(Suppl. B), 1-23
CODEN: MDACAP; ISSN: 0025-7656
PB J. R. Prous, S.A.
DT Journal; General Review
LA English
AB A review with 93 refs. On May 29, 1997, the United States Food and Drug Administration granted final approval for the use of carvedilol in the treatment of mild to moderate congestive heart failure. In this action, the United States joined 20 countries worldwide that have approved carvedilol (Coreg/Kredex) for treatment of hypertension and congestive heart failure. Carvedilol is also approved for the treatment of angina in several countries. Carvedilol is a chem. distinct and pharmacol. unique agent that possesses multiple pharmacol. actions, including nonselective .beta.-**adrenoceptor** blockade, .alpha.1-**adrenoceptor** blockade, potent antioxidant activity, and regulation of genes involved in cardiovascular organ remodeling and apoptosis. Based on this pharmacol. profile, carvedilol is uniquely positioned to inhibit several of the major pathol. processes that drive the progression of congestive heart failure, including: (1) hemodynamics: redn. of preload, afterload and heart rate; (2) neurohormonal: inhibition of the sympathetic nervous system, renin-angiotensin system and endothelin; (3) oxidative stress: scavenging potentially toxic O radicals and restoring endogenous antioxidants; (4) genomic reformatting: suppression of several genes assocd. with pathol. organ remodeling. Thus, carvedilol, through its multiple actions, has the capacity to provide broad cardiovascular organ protection. As a result of these multiple actions, carvedilol, when used in conjunction with std. therapy for heart failure (i.e., diuretics, digoxin, and angiotensin-converting enzyme inhibitors), significantly reduced morbidity, mortality and hospitalization in patients with congestive heart failure of either ischemic or nonischemic (i.e., idiopathic dilated cardiomyopathy) origin, independent of disease severity (mild to moderate) or left ventricular function (ejection fraction). The highly favorable clin. outcomes from the large multicenter clin. trials conducted with carvedilol in the United States and Australia/New Zealand merit a detailed update of the unique mechanisms of action of carvedilol, and a thorough review of the clin. trial results. This review highlights previous exptl. findings with carvedilol as well as more recent data that shed light on the mechanisms by which this drug produces its effects in congestive heart failure. In addn., an update of the results from the large multicenter clin. trials, which

formed the basis for the approval of the drug for the treatment of heart failure, is presented.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of oxidative stress, **cardiac** remodeling and progression of congestive **heart** failure in humans by)

L10 ANSWER 4 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1998:116554 HCAPLUS
DN 128:149150
TI Clinical pharmacology of .beta.-blocker in the treatment of cardiac failure
AU Schmidt, B. M. W.; Wehling, M.; Ertl, G.
CS Inst. Klinische Pharmakologie, Fak. Klin. Med., Ruprecht-Karls-Univ., Mannheim, D-68167, Germany
SO Dtsch. Med. Wochenschr. (1998), 123(7), 171-173
CODEN: DMWOAX; ISSN: 0012-0472
PB Georg Thieme Verlag
DT Journal; General Review
LA German
AB A review with 15 refs. is given, summarizing the results of different clin. trials on .beta.-blockers in the treatment of chronic heart failure. Carvedilol, a combination of .beta.- and .alpha.1-blockers, showed beneficial effects on morbidity and mortality of patients with mild or moderate chronic heart failure, but it is still not generally recommended for patients with severe heart failure.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. pharmacol. of .beta.-blocker in the treatment of **cardiac** failure)

L10 ANSWER 5 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1998:93758 HCAPLUS
DN 128:225946
TI Possible involvement of stress-activated protein kinase signaling pathway and Fas **receptor** expression in prevention of ischemia/reperfusion-induced cardiomyocyte apoptosis by carvedilol
AU Yue, Tian-Li; Ma, Xin-Liang; Wang, Xinkang; Romanic, Anne M.; Liu, Gao-Lin; Louden, Calvert; Gu, Juan-Li; Kumar, Sanjay; Poste, George; Ruffolo, Robert R., Jr; Feuerstein, Giora Z.
CS Department of Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SO Circ. Res. (1998), 82(2), 166-174
CODEN: CIRUAL; ISSN: 0009-7330
PB Williams & Wilkins
DT Journal
LA English
AB Carvedilol, a new vasodilating .beta.-**adrenoceptor antagonist** and a potent antioxidant, produces a high degree of cardioprotection in a variety of exptl. models of ischemic cardiac injury. Recent clin. studies in patients with heart failure have demonstrated that carvedilol reduces morbidity and mortality and inhibits cardiac remodeling. The present study was designed to explore whether the protective effects of carvedilol on the ischemic myocardium include inhibition of apoptosis of cardiomyocytes and, if so, to det. its mechanism of action. Anesthetized rabbits were subjected to 30 min of coronary artery occlusion followed by 4 h of reperfusion. Detection of apoptosis of cardiomyocytes was based on the presence of nucleosomal DNA fragments on agarose gels (DNA ladder) and in situ nick end labeling. Carvedilol (1 mg/kg IV), administered 5 min before reperfusion, reduced the no. of apoptotic

myocytes in the ischemic area from 14.7% to 3.4% (77% redn.). Propranolol, administered at equipotent .beta.-blocking dosage, reduced the no. of apoptotic myocytes to 8.9% (39% redn.). DNA ladders were obsd. in the hearts of all six vehicle-treated rabbits but only one of six carvedilol-treated rabbits. Immunocytochem. anal. of rabbit hearts demonstrated an upregulation of Fas protein in ischemic cardiomyocytes, and treatment with carvedilol reduced both the intensity of staining as well as the area stained. Myocardial ischemia/reperfusion led to a rapid activation of stress-activated protein kinase (SAPK) in the ischemic area but not in nonischemic regions. SAPK activity was increased from 2.1 mU/mg (basal) to 8.9 mU/mg after 30 min of ischemia followed by 20 min of reperfusion. Carvedilol inhibited the activation of SAPK by 53.4%. Under the same conditions, propranolol (1 mg/kg) had no effect on SAPK activation. Thus, carvedilol prevents myocardial ischemia/reperfusion-induced apoptosis in cardiomyocytes possibly by downregulation of the SAPK signaling pathway, by inhibition of Fas **receptor** expression, and by .beta.-adrenergic blockade. The former two actions represent novel and important mechanisms that may contribute to the cardioprotective effects of carvedilol.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stress-activated protein kinase signaling pathway and Fas **receptor** expression may be involved in prevention of ischemia/reperfusion-induced **cardiomyocyte** apoptosis by carvedilol)

L10 ANSWER 6 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1998:45004 HCAPLUS
DN 128:84215
TI Evaluation of intrinsic sympathomimetic activity of bucindolol and carvedilol in rat heart
AU Willette, Robert N.; Mitchell, Marcus P.; Ohlstein, Eliot H.; Lukas, Mary Ann; Ruffolo, Robert R., Jr.
CS Dep. Cardiovascular Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SO Pharmacology (1998), 56(1), 30-36
CODEN: PHMGBN; ISSN: 0031-7012
PB S. Karger AG
DT Journal
LA English
AB Many .beta.-**adrenoceptor antagonists** are weak partial agonists, possessing significant intrinsic sympathomimetic activity (ISA). Under certain conditions, ISA may be deleterious through stimulation of .beta.1- and/or .beta.2-**adrenoceptors** in the heart. Drugs with ISA are particularly problematic in the treatment of congestive heart failure since agents that activate cardiac .beta.-**adrenoceptors**, such as xamoterol, have been assocd. with increases in the incidence of arrhythmia and mortality. Carvedilol was recently approved for the treatment of congestive heart failure, and bucindolol is currently in large clin. trials for this indication. In the present study, the ISA of bucindolol and carvedilol was evaluated in a std. model used to investigate ISA, the pithed rat. Both compds. produced dose-dependent inhibition of the pos.-chronotropic effects of the non-selective .beta.-**adrenoceptor** agonist, isoproterenol, confirming that these drugs are .beta.-**adrenoceptor antagonists**. However, cumulative administration of bucindolol (10-1,000 .mu.g/kg i.v.) in the pithed rat produced a significant dose-related increase in heart rate. The maximal increase in heart rate produced by bucindolol was 44% of that obtained with isoproterenol (90 vs. 205 11 bpm, resp.). In marked contrast, cumulative administration of carvedilol (10-1,000 .mu.g/kg i.v.) had no significant effect on

resting heart rate in the pithed rat. The maximal increase in heart rate elicited by bucindolol (1,000 .mu.g/kg i.v.) was inhibited by treatment with the competitive .beta.-**adrenoceptor antagonist**, propranolol (99 .+-. 8.7 vs. 26 .+-. 2.6 bpm), confirming that the ISA obsd. with bucindolol was mediated through stimulation of myocardial .beta.-**adrenoceptors**. Carvedilol, which had no ISA, **antagonized** the ISA of bucindolol, and was as effective as propranolol in blocking the ISA of bucindolol (99 .+-. 8.7 vs. 27 .+-. 2.3 bpm). In summary, bucindolol and carvedilol are both potent .beta.-**adrenoceptor antagonists** in the pithed rat; however, only bucindolol possesses .beta.-**adrenoceptor**-mediated ISA.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of intrinsic sympathomimetic activity of bucindolol and carvedilol in rat **heart**)

L10 ANSWER 7 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1998:15051 HCAPLUS
DN 128:135932
TI Protective effects of carvedilol in the myocardium
AU Feuerstein, Giora Z.; Bril, Antoine; Ruffolo, Robert R., Jr.
CS Division Pharmacological Sciences, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA
SO Am. J. Cardiol. (1997), 80(11A), 41L-45L
CODEN: AJCDAG; ISSN: 0002-9149
PB Excerpta Medica, Inc.
DT Journal; General Review
LA English
AB A review with 29 refs. Beta blockers have long been used in the treatment of systemic hypertension, where they effectively lower blood pressure and, in so doing, they decrease left ventricular hypertrophy. The sympathetic nervous system is activated in patients with congestive heart failure, and therefore it is logical that .beta. blockers may also provide benefit in these patients. As such, .beta. blockers are currently being evaluated in several large clin. trials in congestive heart failure. One particular drug, carvedilol, is a third-generation vasodilating .beta. blocker that is marketed for the treatment of hypertension. The drug lowers systemic arterial blood pressure without producing reflex tachycardia and preserves renal function. Carvedilol decreases mortality by 65% and decreases hospitalization by 29% in patients with congestive heart failure. The effects of carvedilol in heart failure may result, at least in part, from .beta. blockade as well as vasodilation, the latter resulting from .alpha.1-**adrenoceptor** blockade. Interestingly, carvedilol has a no. of addnl. properties that may also provide benefit in these patients. Carvedilol and several of its metabolites are potent antioxidants that may inhibit catecholamine toxicity resulting from the oxidn. of norepinephrine and the subsequent formation of toxic intermediates, including the generation of reactive oxygen free radicals in the myocardium. A a result of its antioxidant activity, carvedilol also blocks the expression of several genes involved in myocardial damage and cardiac remodeling, and the drug inhibits free radical-induced activation of transcription factors and programmed cell death (apoptosis). Carvedilol is a novel .beta. blocker that is highly effective in the treatment of hypertension and congestive heart failure, and combines in one mol. a no. of important pharmacol. properties.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(Protective effects of carvedilol in the human and lab. animal **myocardium**)

L10 ANSWER 8 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:804677 HCAPLUS
DN 128:110636
TI Second- and third-generation beta-blocking drugs in chronic heart failure
AU Bristow, Michael R.; Abraham, William T.; Yoshikawa, Tsutomu; White, Michel; Hattler, Brack G.; Crisman, Thomas S.; Lowes, Brian D.; Robertson, A. D.; Larrabee, Patti; Gilbert, Edward M.
CS University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SO Cardiovasc. Drugs Ther. (1997), 11(Suppl. 1), 291-296
CODEN: CDTHET; ISSN: 0920-3206
PB Kluwer Academic Publishers
DT Journal
LA English
AB The left-ventricular (LV) functional, hemodynamic, and antiadrenergic effects of metoprolol, bucindolol, and carvedilol have been compared in three concurrent placebo-controlled clin. trials in patients with symptomatic idiopathic dilated cardiomyopathy. All three drugs were well tolerated, all produced at least moderate degrees of .beta.-blockade as assessed by redn. in exercise heart rate, and all increased the left-ventricular ejection fraction. Compared with the .beta.1-selective, second-generation compd. metoprolol, the third-generation compds. bucindolol and carvedilol lowered indexes of adrenergic activity and tended to improve LV function to a greater extent. In patients with chronic heart failure there may be important therapeutic response differences between second- and third-generation beta-blocking agents.
IT **72956-09-3**, Carvedilol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Second- and third-generation beta-blockers in chronic **heart** failure in humans)

L10 ANSWER 9 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:804673 HCAPLUS
DN 128:110226
TI Pharmacology of carvedilol: rationale for use in hypertension, coronary artery disease, and congestive heart failure
AU Ruffolo, Robert R., Jr.; Feuerstein, Giora Z.
CS SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406-0939, USA
SO Cardiovasc. Drugs Ther. (1997), 11(Suppl. 1), 247-256
CODEN: CDTHET; ISSN: 0920-3206
PB Kluwer Academic Publishers
DT Journal; General Review
LA English
AB A review with 77 refs. Carvedilol is a novel, multiple-action cardiovascular drug that is currently approved in many countries for the treatment of hypertension. The redn. in blood pressure produced by carvedilol results primarily from .beta.-**adrenoceptor** blockade and vasodilation, the latter resulting from .alpha.1-**adrenoceptor** blockade. These actions, as well as several of the other activities of carvedilol, are assocd. with cardioprotection in animal models that occurs to a degree that is greater than that obsd. with other drugs. The multiple actions of carvedilol may also provide the underlying rationale for the use of the drug in the treatment of coronary artery disease and congestive heart failure. By virtue of being both a beta-blocker and a

vasodilator, carvedilol significantly decreases myocardial work by reducing all three components of myocardial oxygen demand, namely, heart rate, contractility, and wall tension. The vasodilatory effects of carvedilol reduce afterload, and the resulting decrease in impedance to left ventricular ejection offsets the neg. inotropic effect that would normally result from beta-blockade. As a consequence, stroke vol. and cardiac output are maintained or even increased in animals and in patients with congestive heart failure who are treated with carvedilol. Carvedilol and several of its metabolites are potent antioxidants, and this activity may account, in part, for the cardioprotective effects of the drug obsd. in animal models of acute myocardial ischemia and, in theory, could also serve to protect the myocardium of patients with hypertension, coronary artery disease, and congestive heart failure, in which oxidative stress is now recognized to occur. The antioxidant effects of carvedilol may both inhibit the direct cytotoxic actions of reactive oxygen radicals and prevent oxygen-radical induced activation of transcription factors and genes assocd. with inflammatory and remodeling processes. Accordingly, carvedilol inhibits the gene expression of the intracellular adhesion mol.-1 (ICAM-1), an adhesion mol. for polymorphonuclear leukocytes, which typically infiltrate the myocardium under conditions of ischemia and may exacerbate ischemic injury. The antioxidant activity of carvedilol has been shown to inhibit the oxidn. of low d. lipoprotein (LDL) in vitro, thereby preventing the formation of this cytotoxic and atherogenic form of LDL. It follows, therefore, that in animal models of hyperlipidemia, carvedilol attenuates aortic lipid accumulation and decreases the aortic content of monocytes and foam cells, and at the same time it has been shown to preserve endothelial integrity and function. These actions of carvedilol are not shared by other beta-blockers or by other drugs currently used in the management of hypertension, coronary artery disease, or congestive heart failure. The multiple actions of carvedilol may provide the underlying pharmacol. rationale for the use of this drug in the treatment of patients with coronary artery disease or congestive heart failure, and these actions may account, at least in part, for the redn. in mortality produced by carvedilol in clin. trials involving patients with congestive heart failure. Likewise, these actions of carvedilol may also provide protection, beyond that afforded from redn. in blood pressure, against secondary organ damage in hypertensive patients treated with the drug.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol use in hypertension, coronary artery disease, and congestive **heart** failure in humans and lab. animals)

L10 ANSWER 10 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:726197 HCAPLUS
DN 128:18534
TI Long-term Carvedilol therapy increases parasympathetic nervous system activity in chronic congestive heart failure
AU Goldsmith, Rochelle L.; Bigger, J. Thomas; Bloomfield, Daniel M.; Krum, Henry; Steinman, Richard C.; Sackner-Berstein, Jonathan; Packer, Milton
CS Div. Circulatory Physiol., Div. Cardiol., Coll. Physicians and Surgeons, Columbia Univ., New York, NY, USA
SO Am. J. Cardiol. (1997), 80(8), 1101-1104
CODEN: AJCDAG; ISSN: 0002-9149
PB Excerpta Medica
DT Journal
LA English
AB This study examd. the effects of carvedilol on parasympathetic nervous system activity in congestive heart failure patients already

receiving angiotensin-converting enzyme inhibitors and digoxin. Results suggested that carvedilol markedly increased the vagally mediated variation in RR interval in patients with heart failure. In addn., carvedilol treatment was assocd. with improved ejection fraction, left ventricular filling pressure and other clin. parameters. Improvements in cardiac function and hemodynamics were most marked in patients with the highest pretreatment heart rate. Possible mechanisms of the parasympathetic effects of carvedilol are discussed.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Carvedilol effects on parasympathetic nervous system activity in humans with chronic congestive **heart** failure)

L10 ANSWER 11 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:712443 HCAPLUS
DN 128:9979
TI .beta.-Blockers in congestive heart failure: the pharmacology of carvedilol, a vasodilating .beta.-blocker and antioxidant, and its therapeutic utility in congestive heart failure
AU Feuerstein, Gloria; Ruffolo, Robert R., Jr.
CS Cardiovascular Pharmacol., Smith Kline Beencham Pharmaceuticals, King of Prussia, PA, 19406-0939, USA
SO Adv. Pharmacol. (San Diego) (1998), 42(Catecholamines), 611-615
CODEN: ADPHEL; ISSN: 1054-3589
PB Academic
DT Journal; General Review
LA English
AB A review, with 9 refs. A large, multicenter, double-blind, placebo-controlled clin. trial of carvedilol, a vasodilating .beta.-blocker with antioxidant activity, showed a 65% redn. in mortality and a significant redn. in hospitalization. A multiple action of the drug and cardioprotective effects are discussed.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of carvedilol as vasodilating .beta.-blocker and antioxidant and its therapeutic utility in congestive **heart** failure)

L10 ANSWER 12 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:678202 HCAPLUS
DN 127:325839
TI Carvedilol update IV: prevention of oxidative stress, cardiac remodeling and progression of congestive heart failure
AU Feuerstein, Giora Z.; Shusterman, Neil H.; Ruffolo, Robert R., Jr.
CS SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SO Drugs Today (1997), 33(7), 453-473
CODEN: MDACAP; ISSN: 0025-7656
PB Prous
DT Journal; General Review
LA English
AB A review with 93 refs. On May 29, 1997, the United States Food and Drug Administration granted final approval for the use of carvedilol in the treatment of mild to moderate congestive heart failure. In this action, the United States joined 20 countries worldwide that have approved carvedilol (Coreg/Kredex) for treatment of hypertension and congestive heart failure. Carvedilol is also approved for the treatment of angina in several countries. Carvedilol (Fig. 1) is a chem. distinct and pharmacol. unique agent that possesses multiple pharmacol. actions, including: (1) non-selective .beta.-**adrenoceptor** blockade, (2) .alpha.1-**adrenoceptor** blockade, (3) potent antioxidant activity, and

(4) regulation of genes involved in cardiovascular organ remodeling and apoptosis. Based on this pharmacol. profile, carvedilol is uniquely positioned to inhibit several of the major pathol. processes that drive the progression of congestive heart failure, including: (1) hemodynamics: redn. of preload, afterload and heart rate; (2) neurohormonal: inhibition of the sympathetic nervous system, renin-angiotensin system and endothelin; (3) oxidative stress: scavenging potentially toxic oxygen radicals and restoring endogenous antioxidants; (4) genomic reformatting: suppression of several genes assocd. with pathol. organ remodeling. Thus, carvedilol, through its multiple actions, has the capacity to provide broad cardiovascular organ protection. As a result of these multiple actions, carvedilol, when used in conjunction with std. therapy for heart failure (i.e., diuretics, digoxin, and angiotensin-converting enzyme inhibitors), significantly reduced morbidity, mortality and hospitalization in patients with congestive heart failure of either ischemic or nonischemic (i.e., idiopathic dilated cardiomyopathy) origin, independent of disease severity (mild to moderate) or left ventricular function (ejection fraction). The highly favorable clin. outcomes from the large multicenter clin. trials conducted with carvedilol in the United States and Australia/New Zealand merits a detailed update of the unique mechanisms of action of carvedilol, and a thorough review of the clin. trial results. Accordingly, we will highlight in this update our previous exptl. findings with carvedilol as well as more recent data that shed light on the mechanisms by which this drug produces its effects in congestive heart failure. In addn., an update of the results from the large multicenter clin. trials, which formed the basis for the approval of the drug for the treatment of heart failure, will be presented.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol update IV: prevention of oxidative stress, **cardiac** remodeling and progression of congestive **heart** failure)

L10 ANSWER 13 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:674677 HCAPLUS
DN 127:341551
TI Effects of the novel multiple-action agent carvedilol on severe nephrosclerosis in renal ablated rats
AU Rodriguez-Perez, Jose C.; Losada, Antonio; Anabitarte, Aranzazu; Cabrera, Juan; Llobet, Javier; Palop, Leocadia; Plaza, Celia
CS Research Unit, Hospital Nuestra Senora del Pino, Las Palmas de Gran Canaria, Spain
SO J. Pharmacol. Exp. Ther. (1997), 283(1), 336-344
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB Antihypertensive drugs have differing effects on renal hemodynamics and morphol. We analyzed whether the use of a new beta **adrenoceptor antagonist**, and vasodilator, carvedilol (CVD), slows the progression of nephrosclerosis and whether the renoprotective effect as well as redn. in cardiac hypertrophy is dependent on the degree of blood pressure redn. Fifty-four adult male Sprague-Dawley rats were distributed among five groups: group I served as untreated controls with 5/6 nephrectomy (Nx); group II, sham (no renal ablation or drug treatment); group III, CVD 5 (5/6 Nx and treatment with oral CVD at 5 mg/kg/day); group IV, CVD 10 (5/6 Nx and treatment with oral CVD at 10 mg/kg/day); and group V, CVD 20 (5/6 Nx and treatment with oral CVD at 20 mg/kg/day). Tail-cuff blood pressure and 24-h urine

samples were obtained before and at 3, 5 and 11 wk of treatment with CVD. At the end of the study period, blood was taken to measure serum creatinine, plasma renin activity and CVD levels, as well as the remnant kidney and heart for morphol. studies. There was a significant redn. in 24-h UProtV in all the CVD-treated groups, and it was increasingly evident with the highest dose used. However, only rats receiving doses of 10 and 20 mg/kg/day of CVD exhibited significant decreases in blood pressure. Elevated serum creatinine levels seen in untreated controls were significantly decreased by CVD in treated rats ($P < .01$), indicating that glomerular filtration rate was improved by this drug. This was assocd. with a significant increase in UNav. Concomitant and significant ($P < .01$) decreases in plasma renin activity were obsd. in sham and CVD-treated rats. CVD-treated animals had considerably reduced renal damage ($P < .01$) and cardiac hypertrophy ($P < .01$) compared with untreated controls. These data indicate that CVD is effective in delaying progression of renal damage and provides beneficial effects in the remnant kidney and cardiac hypertrophy, even at nonhypotensive doses.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol effect on nephrosclerosis and **cardiac** hypertrophy in renal ablated rats)

L10 ANSWER 14 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:572416 HCAPLUS
DN 127:242654
TI Focus on carvedilol: a novel .beta.-adrenergic blocking agent for the treatment of congestive heart failure
AU Chen, Bonnie P.; Chow, Moses S. S.
CS School Pharmacy, University Connecticut, Storrs, CT, USA
SO Formulary (1997), 32(8), 795-798, 801-805
CODEN: FORMF9; ISSN: 1082-801X
PB Advanstar
DT Journal; General Review
LA English
AB A review with 54 refs. Carvedilol (Coreg) is a nonselective .beta.-**adrenoreceptor** blocker with vasodilating activity. In addn. to its earlier approval for the treatment of essential hypertension, the drug has recently become the first .beta.-blocking agent cleared in the United States for the treatment of congestive heart failure (CHF). Clin. trials have shown that adding carvedilol to std. CHF therapy significantly reduces the risk of death and hospitalization in patients with mild to moderate CHF. To achieve these results, it is imperative that the dosage of carvedilol be titrated carefully. Because of its documented ability to improve survival and morbidity outcomes, carvedilol is a welcome addn. to the formulary.

IT **72956-09-3**, Coreg
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of congestive **heart** failure with .beta.-blocker carvedilol)

L10 ANSWER 15 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:541743 HCAPLUS
DN 127:242991
TI Increased myocardial oxygen consumption and resting heat production, as measured by microcalorimetry, after propranolol and carvedilol treatment: Is there a partial agonistic effect in the rat?
AU Fagher, B.; Ikomi-Kumm, J.; Monti, M.
CS Department of Cell Biology, University Hospital of Lund, Lund University, S-221 85 Lund, Swed.
SO Thermochim. Acta (1997), 298(1-2), 75-80
CODEN: THACAS; ISSN: 0040-6031

PB Elsevier
DT Journal
LA English
AB This study investigated the influence of.beta.-blockade on the resting heat prodn. of myocardial tissue by microcalorimetry. During one week, propranolol (.beta.1.beta.2-**adrenoceptor antagonist**) was orally given to 14 rats - 5mgkg-1once daily, and carvedilol (.beta.1.beta.2- and.alpha.1-**antagonist**) to eight rats - 3mgkg-1once daily; 36 rats were controls. Thin slices of cardiac tissue, .apprxeq.10 mg, were removed from the apex. Carbogen-satd. Krebs-Ringer bicarbonate buffer with glucose as substrate was pumped through the microcalorimetric ampoule during the measurement at 37.degree.C.Unexpectedly, the mean resting heat prodn. was higher after both propranolol, 1.25mWg-1wet tissue ($p<0.01$, ANOVA) and carvedilol, 1.19mWg-1($p<0.05$) treatments, than in the control group, 1.01mWg-1. The same applied to oxygen consumption. The calcd. anaerobic fractions were 16, 8 and 24% in the resp. groups, but differences were not significant. Also, when added in vitro, propranolol caused an enhanced myocardial resting heat prodn. by an av. of 23%. As resting myocardial metab. contributes to the overall cardiac energetics to a relatively minor extent, the net result of treatment will probably be of only marginal physiol. importance.The expt1. outcome is indicative of a stimulation of resting myocardial metabolic activity after propranolol and carvedilol, rather than a predicted decrease. We hypothesize that the absence of anything to depress in the non-beating heart tissue, reveals a small degree of partial .beta.-agonist activity, possibly via the newly discovered .beta.3-**adrenoceptor**.
IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(increased **myocardial** oxygen consumption and resting heat prodn. after propranolol and carvedilol treatment)

L10 ANSWER 16 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:484786 HCAPLUS
DN 127:144971
TI Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction. A placebo-controlled, randomized trial
AU Basu, Sumit; Senior, Roxy; Raval, Usha; Van Der Does, Reinhard; Bruckner, Thomas; Lahiri, Avijit
CS Department of Cardiology, Northwick Park Hospital and Institute of Medical Research, Harrow, HA1 3 UJ, UK
SO Circulation (1997), 96(1), 183-191
CODEN: CIRCAZ; ISSN: 0009-7322
PB American Heart Association
DT Journal
LA English
AB Evidence of efficacy and safety of .beta.-blockers after thrombolysis for acute myocardial infarction (AMI) is equivocal. Newer .beta.-blockers such as carvedilol have not been tested in this setting. This study investigated the effects of acute (i.v.) and long-term (6 mo, oral) treatment with carvedilol vs. placebo in 151 consecutive patients with AMI. Exercise ECG, ambulatory monitoring, and two-dimensional echocardiog. were performed before hospital discharge and at 3 and 6 mo. All patients were followed up and cardiovascular events recorded. The Cox proportional hazards model was used to compare time from randomization with the occurrence of a cardiovascular event, and Kaplan-Meier survival curves were calcd. Carvedilol was found to be safe, and it significantly reduced cardiac events compared with placebo (18 on carvedilol and 31 on placebo, $P<.02$). Fifty-four patients had heart failure at study entry; 34 received carvedilol. There were no

adverse effects of carvedilol therapy and no excess events in this subgroup. Carvedilol produced significant redns. in heart rate (P<.0001), blood pressure (P<.005) at rest, and rate-pressure product at peak exercise (P<.003), but exercise capacity was unchanged. Left ventricular ejection fraction was not altered significantly by carvedilol, but stroke vol. was higher at pre-hospital discharge examn. (63 vs. 53 mL; P<.01). Diastolic filling of the left ventricle (E/A ratio) was also improved (1.2 vs. 0.9; P<.001). In a subgroup with left ventricular ejection fraction <45% (n=49 patients; 24 on carvedilol and 25 on placebo), carvedilol showed attenuation of remodeling. Carvedilol was well tolerated and safe to use in patients immediately after AMI, including those with heart failure, and significantly improved outcome.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of i.v. and oral carvedilol treatment in acute **myocardial infarction**)

L10 ANSWER 17 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:466906 HCAPLUS
DN 127:130687
TI Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials
AU Heidenreich, Paul A.; Lee, Tina T.; Massie, Barry M.
CS Department of Health Research and Policy, Stanford University, Stanford, CA, USA
SO J. Am. Coll. Cardiol. (1997), 30(1), 27-34
CODEN: JACCDI; ISSN: 0735-1097
PB Elsevier
DT Journal
LA English
AB We sought to evaluate the current evidence for an effect of beta-blockade treatment on mortality in patients with congestive heart failure (CHF). Although numerous small studies have suggested a benefit with beta-blocker therapy in patients with heart failure, a clear survival benefit has not been demonstrated. A recent combined anal. of several studies with the alpha- and beta-adrenergic blocking agent carvedilol demonstrated a significant survival **advantage**; however, the total no. of events was small. Furthermore, it is unclear if previous studies with other beta-blockers are consistent with this findings. Randomized clin. trails of beta-blockade treatment in patients with CHF from Jan. 1975 through Feb. 1997 were identified using a MEDLINE search and a review of reports from scientific meetings. Studies were included if mortality was reported during 3 or more months of follow-up. We identified 35 reports, 17 of which met the inclusion criteria. These studies included 3,039 patients with follow-up ranging from 3 mo to 2 yr. Beta-blockade was assocd. with a trend toward mortality redn. in 13 studies. When all 17 reports were combined, beta-blockade significantly reduced all-cause mortality (random effect odds ratio [OR] 0.69, 95% confidence interval [CI] 0.54 to 0.88). A trend toward greater treatment effect was noted for nonsudden cardiac death (OR 0.58, 95% CI 0.40 to 0.83) compared with sudden cardiac death (OR 0.84, 95% CI 0.59 to 1.2). Similar redns. in mortality were obsd. for patients with ischemic (OR 0.69, 95% CI 0.49 to 0.98) and nonischemic cardiomyopathy (OR 0.69, 95% CI 0.47 to 0.99). The survival benefit was greater for trials of the drug carvedilol (OR 0.54, 95% CI 0.36 to 0.81) than for noncarvedilol drugs (OR 0.82, 95% CI 0.60 to 1.12); however, the difference did not reach statistical significance (p = 0.10). Pooled evidence suggests that beta-blockade reduces all-cause mortality in patients with CHF. Addnl. trials are required to det. whether carvedilol differs in its effect from other agents.

IT **72956-09-3**, Carvedilol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of beta-blockade on mortality in patients with **heart** failure)

L10 ANSWER 18 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:463139 HCAPLUS
DN 127:116962
TI Carvedilol: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders
AU Dunn, Christopher J.; Lea, Andrew P.; Wagstaff, Antona J.
CS Adis International Limited, Auckland, N. Z.
SO Drugs (1997), 54(1), 161-188
CODEN: DRUGAY; ISSN: 0012-6667
PB Adis
DT Journal; General Review
LA English
AB A review with 179 refs. Carvedilol competitively blocks .beta.1, .beta.2 and .alpha.1 **receptors**. The drug lacks sympathomimetic activity and has vasodilating properties that are exerted primarily through .alpha.1-blockade. Animal models indicate that carvedilol confers protection against myocardial necrosis, arrhythmia and cell damage caused by oxidizing free radicals, and the drug has no adverse effects on plasma lipid profiles. Recent data have confirmed the antihypertensive efficacy of carvedilol in patients with mild to moderate essential hypertension. Carvedilol has similar efficacy to other .beta.-blocking agents, calcium **antagonists**, ACE inhibitors and hydrochlorothiazide. Carvedilol also improves exercise tolerance and ischemic symptoms in patients with stable angina pectoris. Significant redns. in serious cardiac events after acute myocardial infarction and in frequency and severity of ischemic events in patients with unstable angina have also been demonstrated. Interest in the use of carvedilol in patients with congestive heart failure (CHF) has culminated in the publication of a cumulative anal. of data from 1094 patients with mild to severe CHF who participated in the US Carvedilol Heart Failure Study Program (4 trials). After a median follow-up of 6.5 mo, a significant overall redn. in mortality relative to placebo (3.2 vs 7.8%) was revealed in patients who had received carvedilol 6.25 to 50 mg twice daily (plus diuretics and ACE inhibitors). All-cause mortality, risk of hospitalization for cardiovascular reasons and hospitalization costs were also reduced significantly (by 65, 28% and 62%, resp.) in these trials. In addn., the Australia and New Zealand Heart Failure Research Collaborative Group showed a 26% redn. in the combined risk of death or hospitalization with carvedilol 12.5 to 50 mg/day relative to placebo after a mean 19-mo follow-up period in 415 patients with CHF (relative risk 0.74). Adverse events with carvedilol appear to be less frequent than with other .beta.-blocking agents, are dosage-related and are usually seen early in therapy. Events most commonly reported are related to the vasodilating (postural hypotension, dizziness and headaches) and the .beta.-blocking (dyspnoea, bronchospasm, bradycardia, malaise and asthenia) properties of the drug. Carvedilol appears to date to have little effect on the incidence of worsening heart failure. Concomitant administration of carvedilol with some medications requires monitoring. Carvedilol is therefore likely to have a beneficial role in the management of controlled CHF, but further clin. studies are required to show the place of .beta.-**adrenoceptor** blocking therapy in general in this indication, and the position of carvedilol relative to other similar agents. Carvedilol is also confirmed as effective in the management of mild to moderate hypertension and ischemic heart disease.
IT **72956-09-3**, Carvedilol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(carvedilol: a reappraisal of its pharmacol. properties and therapeutic use in **cardiovascular** disorders)

L10 ANSWER 19 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:458367 HCAPLUS
DN 127:171295
TI Carvedilol retards sudden loss of contraction during early regional myocardial ischemia in feline hearts
AU Brunvand, Herald; Grong, Ketil
CS Surgical Research Laboratory, Dep. of Surgery, Haukeland University Hospital, Bergen, 5021, Norway
SO J. Pharmacol. Exp. Ther. (1997), 282(1), 363-368
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB The purpose of our study was to investigate whether loss of myocardial contraction immediately after coronary occlusion was nonuniform, and if pretreatment with carvedilol, a vasodilating nonselective .beta.-**adrenoceptor antagonist**, could retard loss of contraction after coronary artery occlusion. Feline hearts were subjected to acute regional ischemia by total occlusion of the left anterior descending coronary artery. The animals were either treated with vehicle (control group) or with carvedilol 1 mg/kg i.v. before left anterior descending coronary artery occlusion (in each group). Regional contraction in the left anterior descending coronary artery perfused region of the heart was studied by cross-oriented sonomicrometry. In control animals, circumferential (subepicardial) contraction ceased after 10 s, whereas longitudinal (subendocardial) contraction ceased immediately after left anterior descending coronary artery occlusion. Loss of contraction in animals treated with carvedilol was significantly slower compared to controls. Circumferential contraction ceased between 30 s and 1 min, whereas longitudinal contraction ceased after 20 s. In conclusion, loss of contraction during the first seconds after coronary occlusion was nonuniform, with most rapid dysfunction in the subendocardium. Pretreatment with carvedilol retarded loss of contraction in both axes.
IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol retards sudden loss of contraction during early regional **myocardial** ischemia in feline **hearts**
)

L10 ANSWER 20 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:281503 HCAPLUS
DN 127:44737
TI Effects of the .alpha.-/.beta.-blocking agent carvedilol on hepatic and systemic hemodynamics in patients with cirrhosis and portal hypertension
AU Sekiyama, Tatsuya; Komeichi, Hirokazu; Nagano, Tomoo; Ohsuga, Masaru; Terada, Hideto; Katsuta, Yasumi; Satomura, Katsuaki; Aramaki, Takumi
CS First Department Internal Medicine, Nippon Medical School, Tokyo, 113, Japan
SO Arzneim.-Forsch. (1997), 47(4), 353-355
CODEN: ARZNAD; ISSN: 0004-4172
PB Cantor
DT Journal
LA English
AB The effect of carvedilol (CAS **72956-09-3**, Artist) was evaluated on hepatic and systemic hemodynamics in 10 patients with portal hypertension. After administration of carvedilol, the

hepatic venous pressure gradient (HVPG) decreased from 15.9 to 13.3 mmHg at 60 min (-15%) and to 12.9 mmHg at 90 min (-17%). Only 5 patients showed a decrease of HVPG by > 20% at 60 or 90 min. The estd. hepatic blood flow (EHBF) was not reduced. In contrast, **heart** rate, mean arterial pressure, and **cardiac** index (CI) were reduced at 90 min, while total systemic vascular resistance was not altered. The redn. of HVPG was correlated with the decrease of CI. The portal hypotensive effect of carvedilol resulted from a redn. of CI.

L10 ANSWER 21 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:272669 HCAPLUS
DN 126:325251
TI Nonselective .beta.-adrenergic blockade with carvedilol does not hinder the benefits of exercise training in patients with congestive heart failure
AU Demopoulos, Laura; Yeh, Michael; Gentilucci, Marco; Testa, Marco; Bijou, Rachel; Katz, Stuart D.; Mancini, Donna; Jones, Margaret; Lejemtel, Thierry H.
CS Department of Medicine, Division of Cardiology, The Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SO Circulation (1997), 95(7), 1764-1767
CODEN: CIRCAZ; ISSN: 0009-7322
PB American Heart Association
DT Journal
LA English
AB Long-term .beta.-adrenergic blockade does not appear to be assocd. with drug-induced training in patients with congestive heart failure (CHF); whether exercise training can increase peak aerobic capacity in patients with CHF who are treated with .beta.-adrenergic blockers is currently unknown. We studied 23 patients with CHF who were treated with carvedilol or propranolol in addn. to ACE inhibitors, furosemide, and digoxin. Of the patients treated with carvedilol, 8 underwent exercise training and 8 remained sedentary. All 7 patients treated with propranolol underwent exercise training. Peak oxygen consumption (mL.cntdot.kg-1.cntdot. min-1) was serially measured in trained and sedentary patients. Peak reactive hyperemia (mL.cntdot.min-1.cntdot.100 mL-1) was detd. in the calf and forearm immediately before and after 12 wk of training. The peak oxygen consumption of trained patients treated with either carvedilol or propranolol increased from 12.9.+-.1.4 to 16.0.+-.1.6 (P<.001) and 12.4.+-.1.0 to 15.7.+-.0.9 (P<.001) mL.cntdot.kg-1.cntdot.min-1, resp., whereas it did not change in the sedentary patients. Peak reactive hyperemia increased significantly in the calves but not the forearms of trained patients. Long-term, nonselective .beta.-adrenergic blockade with carvedilol or propranolol does not prevent patients with CHF from deriving systemic and regional benefits from phys. training.
IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonselective .beta.-adrenergic blockade with carvedilol does not hinder the benefits of exercise training in patients with congestive **heart** failure)

L10 ANSWER 22 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:182565 HCAPLUS
DN 126:258781
TI Randomized, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischemic heart disease
AU MacMahon, S.; Sharpe, N.; Doughty, R.; Krum, H.; Tonkin, A.; Trotter, A.; Burton, R.; Garrett, J.; Lane, G.; Owensby, D.; Ryan, J.; Shepherd, J.; Singh, B.; Jackson, B.; Rudge, G.; Stephensen, J.; Woodhouse, S.; Davidson, P.; Turner, J.; Walsh, W.; Bradbury, J.;

Hamer, A.; Cross, D.; Hall, C.; Kimber, V.; Spaulding, C.; Thomson, A.; Croot, M.; Thompson, P. L.; Horowitz, J.; Leslie, S.; Zhang, Y.; Colquhoun, D.; Hicks, B.; Jeffery, I.; Taverner, P.; Bond, C.; Doughty, R.; Murphy, J.; Sharpe, N.; Hall, C.; Ikram, H.; Richards, M.; Low, C.; Scott, D.; Brown, G.; Lewis, G.; Bruning, J.; Nairn, L.; Clayton, A.; Crawford, J.; McAlister, H.

CS Austin Hosp., Melbourne, Australia

SO Lancet (1997), 349(9049), 375-380
CODEN: LANCAO; ISSN: 0140-6736
PB Lancet
DT Journal
LA English

AB In patients with heart failure, .beta.-blocker therapy improves left-ventricular function after 3-6 mo of treatment, but effects of such treatment on symptoms and exercise performance are inconsistent, and the longer-term effects on death and other serious clin. events remain uncertain. We have investigated these issues in a double-blind, placebo-controlled, randomized trial of the .beta.-adrenergic blocker carvedilol (which also has .alpha.1-blocking properties). 415 Patients with chronic stable heart failure were randomly assigned treatment with carvedilol (207) or matching placebo (208). At baseline, 6 mo, and 12 mo, we measured left-ventricular ejection fraction, left-ventricular dimensions, treadmill exercise duration, 6 min walk distance, New York Heart Assocn. (NYHA) class, and specific activity scale (SAS) score. Double-blind follow-up continued for an av. of 19 mo, during which all deaths, hospital admissions, and episodes of worsening heart-failure were documented. After 12 mo, left-ventricular ejection fraction had increased by 5.cntdot.3% (2p<0.cntdot.0001) and end-diastolic and end-systolic dimensions had decreased by 1.cntdot.7 mm (2p=0.cntdot.06) and 3.cntdot.2 min (2p=0.cntdot.001), resp., in the carvedilol group compared with the placebo group. During the same period that were no clear changes in treadmill exercise duration, 6 min walk distance, NYHA class, or SAS score. After 19 mo, the frequency of episodes of worsening heart failure was similar in the carvedilol and placebo groups (82 vs 75; relative risk 1.cntdot.12 [95% Cl 0.cntdot.82-1.cntdot.53]) but the rate of death or hospital admission was lower in the carvedilol group than in the placebo group (104 vs 131; relative risk 0.cntdot.74[0.cntdot.57-0.cntdot.95]). The beneficial effects of carvedilol on left-ventricular function and size were maintained for at least a year after the start of treatment, but carvedilol had no effect on exercise performance, symptoms, or episodes of worsening heart failure. There was no overall redn. in events resulting in death or hospital admission, and a year of treatment with carvedilol resulted in the avoidance of one such serious event among every 12-13 (SE-5) of these patients with chronic stable heart failure.

IT **72956-09-3**, Carvedilol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol for humans with congestive **heart** failure due to ischemic **heart** disease)

L10 ANSWER 23 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:54029 HCAPLUS
DN 126:84392
TI Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure
AU Bristow, Michael R.; Gilbert, Edward M.; Abraham, William T.; Adams, Kirkwood F.; Fowler, Michael B.; Hershberger, Ray E.; Kubo, Spencer H.; Narahara, Kenneth A.; Ingersoll, Henry; Krueger, Steven; Young, Sarah; Shusterman, Neil
CS Univ. Colorado Health Sciences Center, Denver, CO, USA

SO Circulation (1996), 94(11), 2807-2816
CODEN: CIRCAZ; ISSN: 0009-7322
PB American Heart Association
DT Journal
LA English
AB We conducted a multicenter, placebo-controlled trial designed to establish the efficacy and safety of carvedilol, a "third-generation" .beta.-blocking agent with vasodilator properties, in chronic heart failure. Three hundred forty-five subjects with mild to moderate, stable chronic heart failure were randomized to receive treatment with placebo, 6.25 mg BID carvedilol (low-dose group), 12.5 mg BID carvedilol (medium-dose group), or 25 mg BID carvedilol (high-dose group). After a 2- to 4-wk up-titrn. period, subjects remained on study medication for a period of 6 mo. The primary efficacy parameter was submaximal exercise measured by two different techniques, the 6-min corridor walk test and the 9-min self-powered treadmill test. Carvedilol had no detectable effect on submaximal exercise as measured by either technique. However, carvedilol was assocd. with dose-related improvements in LV function (by 5, 6, and 8 ejection fraction [EF] units in the low-, medium-, and high-dose carvedilol groups, resp., compared with 2 EF units with placebo, P <.001 for linear dose response) and survival (resp. crude mortality rates of 6.0%, 6.7%, and 1.1% with increasing doses of carvedilol compared with 15.5% in the placebo group, P<.001). When the three carvedilol groups were combined, the all-cause actuarial mortality risk was lowered by 73% in carvedilol-treated subjects (P<.001). Carvedilol also lowered the hospitalization rate (by 58% to 64%, P=.01) and was generally well tolerated. In subjects with mild to moderate heart failure from systolic dysfunction, carvedilol produced dose-related improvements in LV function and dose-related redns. in mortality and hospitalization rate.
IT **72956-09-3**, Carvedilol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol produces dose-related improvements in left ventricular function and survival in humans with chronic **heart** failure)

L10 ANSWER 24 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1997:54028 HCAPLUS
DN 126:84353
TI Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart
AU Gilbert, Edward M.; Abraham, William T.; Olsen, Stephanie; Hattler, Brack; White, Michel; Mealy, Patrice; Larrabee, Patti; Bristow, Michael R.
CS School Medicine, Univ. Utah, Salt Lake City, UT, USA
SO Circulation (1996), 94(11), 2817-2825
CODEN: CIRCAZ; ISSN: 0009-7322
PB American Heart Association
DT Journal
LA English
AB The basic pharmacol. of the third-generation .beta.-blocking agent carvedilol differs considerably from second-generation compds. such as metoprolol. Moreover, carvedilol may produce different, i.e., more favorable, clin. effects in chronic heart failure. For these reasons, the authors compared the effects of carvedilol and metoprolol on adrenergic activity, **receptor** expression, degree of clin. .beta.-blockade, hemodynamics, and left ventricular function in patients with mild or moderate chronic heart failure. The effects of carvedilol vs. metoprolol were compared in two

concurrent placebo-controlled trials with carvedilol or metoprolol that had common substudies focused on adrenergic, hemodynamic, and left ventricular functional measurements. All subjects in the substudies had chronic heart failure resulting from idiopathic dilated cardiomyopathy. Carvedilol at 50 to 100 mg/d produced redns. in exercise heart rate that were similar to metoprolol at 125 to 150 mg/d, indicating comparable degrees of .beta.-blockade. Compared with metoprolol, carvedilol was assocd. with greater improvement in New York Heart Assocn. functional class. Although there were no significant differences in hemodynamic effects between the carvedilol and metoprolol active-treatment groups, carvedilol tended to produce relatively greater improvements in left ventricular ejection fraction, stroke vol., and stroke work compared with changes in the resp. placebo groups. Carvedilol selectively lowered coronary sinus norepinephrine levels, an index of cardiac adrenergic activity, whereas metoprolol did not lower coronary sinus norepinephrine and actually increased central venous norepinephrine levels. Finally, metoprolol was assocd. with an increase in cardiac .beta.-**receptor** d., whereas carvedilol did not change cardiac .beta.-**receptor** expression. The third-generation .beta.-blocking agent carvedilol has substantially different effects on left ventricular function, hemodynamics, adrenergic activity, and .beta.-**receptor** expression than does the second-generation compd. metoprolol. Some or all of these differences may explain the apparent differences in clin. results between the two compds.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol vs. carvedilol in humans with a failing **heart**)

L10 ANSWER 25 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:756501 HCAPLUS
DN 126:14529
TI Carvedilol improves function and reduces infarct size in the feline myocardium by protecting against lethal reperfusion injury
AU Brunvand, Harald; Froeyland, Livar; hexeberg, Erik; rynning, Stein Erik; Berge, Rolf K.; Grong, Ketil
CS Dep. Surgery, Univ. Bergen, Bergen, N-5021, Norway
SO Eur. J. Pharmacol. (1996), 314(1/2), 99-107
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier
DT Journal
LA English
AB This study examd. the effect of carvedilol, a vasodilating .beta.-**adrenoceptor antagonist** and antioxidant, on lethal reperfusion injury in feline hearts subjected to 40 min of regional ischemia and 180 min of reperfusion. 30 Open chest anesthetized cats were randomized into three groups. A control group was compared with a group given carvedilol before coronary artery occlusion and a group given carvedilol immediately before and during early reperfusion. Regional myocardial function was measured by sonomicrometry. Infarct size was detd. by staining the left ventricle with tri-Ph tetrazolium chloride. Myocardial blood flow was measured by radiolabeled microspheres. Tissue levels of glutathione were measured after reperfusion. Infarct size was significantly reduced compared to control both when carvedilol was given before ischemia (0.2.+-.0.1 vs. 17.6.+-.3.6%) and when given immediately before reperfusion (3.7.+-.1.3 vs. 17.6.+-.3.6%). Regional shortening improved significantly and the incidence of ventricular fibrillation during early reperfusion was reduced in both groups treated with carvedilol compared to control. Oxidized glutathione did not differ between groups in the post-ischemic

myocardium. This study supports that lethal reperfusion injury is a significant phenomenon. Furthermore, carvedilol reduces infarct size and reperfusion arrhythmias, and improves post-ischemic regional myocardial function by protecting against both ischemic and lethal reperfusion injury. The present study does not answer whether it is the non-selective .beta.- or .alpha.1-**adrenoceptor antagonism**, the antiarrhythmic or the antioxidant actions of carvedilol that is responsible for the protective effect.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol improves function and reduces **infarct** size in feline **myocardium** by protecting against lethal reperfusion injury)

L10 ANSWER 26 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:730166 HCAPLUS
DN 126:14188
TI Carvedilol: a new paradigm for the treatment of congestive heart failure
AU Bril, Antoine; Feuerstein, Giora Z.; Ruffolo, Robert R., Jr.
CS Div. Pharmacological Sci., SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SO Expert Opin. Invest. Drugs (1996), 5(11), 1523-1529
CODEN: EOIDER; ISSN: 0967-8298
PB Ashley Publications
DT Journal; General Review
LA English
AB A review with 39 refs. Carvedilol is a vasodilating .beta.-blocker with antioxidant activity and is currently approved for use in hypertension, angina, and congestive heart failure in many countries. Carvedilol is a nonselective .beta.1- and .beta.2-**adrenoceptor antagonist**, an .alpha.1-**adrenoceptor antagonist** (which produces vasodilation), and a potent antioxidant. The antioxidant actions of carvedilol have been demonstrated both in vitro and in vivo, including humans at therapeutic doses of the drug. Carvedilol possesses cardioprotective actions that result from the potent antiischemic, antiarrhythmic, and anti-apoptotic effects of the drug that have been demonstrated in a variety of exptl. models of myocardial injury. In Phase III clin. trials in patients with congestive heart failure, carvedilol has been shown to reduce mortality by 65% and to reduce hospitalization significantly.

IT **72956-09-3**, Carvedilol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol as new paradigm for treatment of congestive **heart** failure in human and lab. animals)

L10 ANSWER 27 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:702443 HCAPLUS
DN 126:152560
TI Chronic carvedilol reduces mortality and renal damage in hypertensive stroke-prone rats
AU Barone, Frank C.; Nelson, Allen H.; Ohlstein, Eliot H.; Willette, Robert N.; Sealey, Jean E.; Laragh, John H.; Campbell, Wallace G., Jr.; Feuerstein, Giora Z.
CS Dep. Cardiovascular Pharmacol., SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA
SO J. Pharmacol. Exp. Ther. (1996), 279(2), 948-955
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English

AB The effects of carvedilol, a novel vasodilating .beta.-blocker and antioxidant, and propranolol on survival, neurobehavioral deficits, cardiovascular parameters, plasma renin, plasma aldosterone levels and renal pathol. were detd. in stroke-prone spontaneously hypertensive rats. Stroke-prone spontaneously hypertensive rats were allowed access to 1% NaCl as the drinking soln. and a high fat diet supplemented with carvedilol (1200 or 2400 ppm) or propranolol (2400 ppm). The control group consisted of stroke-prone spontaneously hypertensive rats placed on the same diet with no drug supplement. Animals fed propranolol had a blood level of 864 ng/mL, whereas carvedilol-fed animals had blood levels of 24 ng/mL at 1200 ppm and 471 ng/mL at 2400 ppm. Carvedilol and propranolol treatment resulted in significant beta **adrenoceptor** blockade. Both compds. reduced heart rate, but had no significant effects on systolic arterial blood pressure. Carvedilol- and propranolol-treated animals also exhibited significant, prolonged protection from neurobehavioral deficits and mortality. Elevated plasma renin activity and aldosterone levels seen in untreated controls were significantly decreased by propranolol, and to a considerably greater extent by the same dose of carvedilol. Carvedilol decreased renal histopathol. damage and cardiac hypertrophy to a greater extent than propranolol (at equal doses). Both carvedilol- and propranolol-treated animals had considerably reduced renal damage at 18 wk of treatment. Carvedilol reduced renal damage more than propranolol. In addn., the lower (1200 ppm) dose of carvedilol, which decreased neurobehavioral deficits and mortality, had no significant effects on organ mass or renal function, but significantly reduced renal damage. These data indicate that both beta **adrenoceptor** blockers, esp. carvedilol to a considerably greater degree, convey significant protection in a genetic model of severe hypertension that results in renal and cardiovascular organ pathol., neurobehavioral deficits and premature death.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protective effects of .beta.-blockers carvedilol and propranolol against renal and **cardiovascular** organ pathol. in stroke-prone spontaneously hypertensive rats)

L10 ANSWER 28 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:658281 HCAPLUS
DN 125:317250
TI A hydroxylated analog of the .beta.-**adrenoceptor antagonist**, carvedilol, affords exceptional antioxidant protection to postischemic rat hearts
AU Kramer, Jay H.; Weglicki, William B.
CS Departments Medicine & Physiology, George Washington Univ. Medical Center, Washington, DC, 20037, USA
SO Free Radical Biol. Med. (1996), 21(6), 813-825
CODEN: FRBMEH; ISSN: 0891-5849
DT Journal
LA English
AB The antioxidant and cardioprotective effects of the .beta.-**adrenoceptor antagonist**, carvedilol, and its hydroxylated analog, BM-910228, were compared using the postischemic rat heart model. Hearts were infused with either agent (0.01, 0.10, or 10 nM final, or drug-free infusate) for 10 min prior to 30 min global ischemia, and also during the initial 15 min of reperfusion. Recovery of postischemic hemodynamic parameters (left ventricular systolic and developed pressures, mean diastolic pressure, cardiac output, coronary flow rate, and cardiac pressure-vol. work), and the extent of postischemic tissue lactate dehydrogenase (LDH) loss, lipid hydroperoxide (LOOH) formation, and lipid peroxidn.

(LPO)-derived free radical prodn. were assessed and compared among the treatment groups. The depressive pharmacol. properties (.beta.- and .alpha.-blockade) of both agents masked the extent of postischemic hemodynamic recovery, except at the lowest dose (10 pM) of the analog, which provided significant improvements in systolic and developed pressures, and cardiac work. Treatment with both agents provided significant dose-dependent redns. in postischemic LOOH formation and lipid alkoxyl radical prodn., as detd. by ESR spectroscopy and .alpha.-phenyl-tert-Bu nitrone (PBN) spin trapping (PBN/alkoxyl adduct hyperfine splitting .alpha.N = 13.63 G and .alpha.H = 1.93 G). Although both agents reduced oxidative injury, the hydroxylated analog was clearly the superior antioxidant (equipotent at doses two to three orders of magnitude lower) compared to the parent compd. This was also reflected with respect to drug-mediated improvement in myocardial preservation (reduced LDH release), which paralleled the antioxidant protective effects. Because neither agent displayed significant primary radical scavenging ability at doses (.ltoreq. 10 nM), which did provide substantial inhibition of postischemic LOOH and alkoxyl formation, our data suggest that the antioxidant properties of carvedilol and its analog are mediated primarily through a LPO chain-breaking mechanism. Moreover, the significant antioxidant protection afforded by the analog BM-910228 at subnanomolar levels places this agent into an exclusive category reserved for exceptionally potent antioxidants.

IT **72956-09-3**, Carvedilol **146574-43-8**, BM 910228
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydroxylated analog of carvedilol affords exceptional antioxidant protection to postischemic rat **hearts**)

L10 ANSWER 29 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:426657 HCAPLUS
DN 125:104705
TI Meta-analysis of the use of low-dose beta-adrenergic blocking therapy in idiopathic or ischemic dilated cardiomyopathy
AU Zarembski, Dawn G.; Nolan, Paul E. Jr.; Slack, Marion K.; Lui, Charles Y.
CS Chicago College Pharmacy, University Arizona, Tucson, AZ, 85721, USA
SO Am. J. Cardiol. (1996), 77(14), 1247-1250
CODEN: AJCDAG; ISSN: 0002-9149
DT Journal
LA English
AB Prospective, randomized, placebo-controlled trials were gathered from reviews and data for low-dose beta-adrenergic blocking therapy in idiopathic or ischemic dilated cardiomyopathy evaluated.
IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(meta-anal. of low-dose beta-adrenergic blockers use in idiopathic or ischemic dilated **cardiomyopathy** treatment)

L10 ANSWER 30 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:308426 HCAPLUS
DN 125:947
TI The preventative effects of vasodilating beta-blockers in cardiovascular disease
AU Raftery, E. B.
CS Institute Medical Research, Northwick Park Hospital, Harrow, UK
SO Eur. Heart J. (1996), 17(Suppl. B), 30-38
CODEN: EHJODF; ISSN: 0195-668X
DT Journal
LA English

AB The beta-blocking drugs are known to modify the course of hypertensive and atherosclerotic heart disease and significantly reduce the mortality and morbidity assocd. with these diseases. The place of vasodilating beta-blocking drugs, of which carvedilol is an example, has not been so clear, although they have obvious theor. **advantages**. We performed a study on 12 hypertensive subjects using the technique of continuous ambulatory intra-arterial blood pressure recording which demonstrated that carvedilol (50 mg bid) achieved satisfactory blood pressure control throughout the full 24 h cycle. The addn., there was a marked redn. in left ventricular end-systolic and end-diastolic vols. with prolonged administration, suggesting a decrease in heart size, confirmed in other studies. A second study in patients with chronic stable angina and impaired left ventricular wall motion showed that carvedilol 25 mg bid not only improved exercise tolerance, but also reduced heart size, improved left ventricular ejection fraction, and abolished wall motion abnormalities. These results prompted a further study in 17 patients with chronic ischemic heart failure. The hemodynamic and clin. responses to i.v. carvedilol followed by the oral drug 50 mgm b.i.d. for 8 wk were studied. There was an improvement in all hemodynamic indexes, although postural hypotension necessitated withdrawing two patients and clin. deterioration was evident in two others. The beneficial effects of carvedilol were considered to be related to the combined redn. in afterload and inhibition of neurohumoral activation. These results have been confirmed in placebo-controlled, double-blind studies from other workers.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preventative effects of vasodilating beta-blockers in humans with **cardiovascular** disease)

L10 ANSWER 31 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:308425 HCAPLUS
DN 125:104
TI Carvedilol, a novel vasodilating beta-blocker with the potential for cardiovascular organ protection
AU Feuerstein, G. Z.; Ruffolo, R. R. Jr
CS Division Pharmacological Sciences, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SO Eur. Heart J. (1996), 17(Suppl. B), 24-29
CODEN: EHJODF; ISSN: 0195-668X
DT Journal; General Review
LA English
AB A review with 24 refs. Carvedilol is a vasodilating .beta.-blocker currently marketed for the treatment of mild to moderate hypertension and application is being filed to the FDA for treatment of congestive heart failure. Carvedilol reduces peripheral vascular resistance by blocking arterial .alpha.1-**adrenoceptors**, thereby producing vasodilation, while preventing reflex tachycardia by blocking cardiac .beta.1- and .beta.2-**adrenoceptors**. In addn. to the safety and efficacy of carvedilol as an antihypertensive agent, exptl. studies indicate that carvedilol also provides significant cardioprotection in animal models of acute myocardial infarction as well as protection against the vascular remodelling that occurs following injury of the vasculature. Recent pharmacol. studies have uncovered several novel properties of carvedilol which may function to protect the heart and vasculature from chronic pathol. processes, such as ischemia, atherosclerosis and the remodelling that occurs in the heart and blood vessels as a consequence of pressure overload, injury or shear stress. Specifically, carvedilol, likely as a result of the carbazol moiety, is a potent anti-oxidant. In physicochem., biochem. and cellular

assays, carvedilol and several of its metabolites inhibit lipid peroxidn., scavenge oxygen free radicals, inhibit the formation of reactive oxygen radicals and prevent the depletion of endogenous antioxidants, such as vitamin E and glutathione. Moreover, carvedilol blocks the oxidn. of low-d. lipoproteins (LDL), and thereby prevents the formation of oxidized-LDL which is believed to stimulate foam cell formation and augment the development of atherosclerotic plaque. The ability of carvedilol to prevent the formation of oxidized LDL, in addn. to the general anti-oxidant properties of the compd., results in the protection of the endothelium from oxygen free radical injury, and thereby prevents the subsequent events triggered by endothelial damage. Recently, carvedilol has also been shown to inhibit vascular smooth muscle cell proliferation and migration. Because carvedilol can inhibit vascular smooth muscle cell proliferation induced by a wide variety of mitogens (e.g. growth factors, angiotensin II, endothelin, thrombin), it is likely that the site of inhibition occurs at some point beyond the specific mitogen **receptors**, possibly at a distal common pathway that affects the smooth muscle cell cycle. These unique activities of carvedilol have also been confirmed in vivo in a rat model of neointimal formation following vascular injury by balloon angioplasty, where vascular smooth muscle cell migration and proliferation are the key processes involved in the formation of neointima leading to vascular stenosis. In this model, carvedilol suppressed neointimal growth to a remarkable extent (>85% inhibition of neointimal formation) at a dose that is similar to the antihypertensive dose used clin. in hypertensive patients. Taken together, these unique multiple actions of carvedilol provide not only for adequate control of elevated blood pressure, but may also provide for protection of the heart and vasculature from secondary damage due to hypertension itself, as well as from other causes, such as ischemia, pressure overload, shear stress, vascular injury and atherosclerosis.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol as novel vasodilating beta-blocker with potential for **cardiovascular** organ protection)

L10 ANSWER 32 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:308421 HCAPLUS
DN 125:103
TI Cardiac adrenergic **receptor** effects of carvedilol
AU Yoshikawa, T.; Port, J. D.; Asano, K.; Chidiak, P.; Bouvier, M.; Dutcher, D.; Roden, R. L.; Minobe, W.; Tremmel, K. D.; Bristow, M. R.
CS Health Sciences Center, University Colorado, Denver, CO, 80262, USA
SO Eur. Heart J. (1996), 17(Suppl. B), 8-16
CODEN: EHJODF; ISSN: 0195-668X
DT Journal; General Review
LA English
AB A review with 37 refs. Carvedilol is an **adrenoceptor antagonist** which modulates the activity not only of .beta.1 and .beta.2 but also of .alpha.1 adrenergic **receptors** present on the cell surface membrane of the human cardiac myocyte. In the heart, carvedilol has approx. 7 times higher potency for .beta.1 and .beta.2 **adrenoceptors**, but in the doses 50-100 mg.day-1 used in clin. practice, it is essentially non-selective. In human myocardial prepns. and in cultured heart cells, carvedilol has no intrinsic sympathomimetic activity but is able to identify high affinity agonist-binding **receptors** whose pharmacol. signature is redn. in binding by incubation with guanine nucleotides (guanine nucleotide-modulatable binding). This property is more prominent for the human .beta.2 than for the .beta.1

adrenoceptor. The property of guanine nucleotide-modulatable binding for carvedilol and structurally related bucindolol correlates with their ability to directly down-regulate .beta.1-like **receptors** present in cultured chick myocytes, and with a lack of reversal of down-regulation of cardiac .beta.-**receptors** in patients with heart failure. Carvedilol does not exhibit high levels of inverse agonist activity, which may contribute to its good tolerability in subjects with heart failure. These data indicate that carvedilol produces a high degree of adrenergic **receptor** blockade in the failing human heart, and does not re-sensitize the .beta.-**receptor** pathway to stimulation by adrenergic agonists.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol effect on **cardiac** adrenergic **receptors**)

L10 ANSWER 33 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1996:234542 HCAPLUS
DN 124:278649
TI Carvedilol, a new beta **adrenoreceptor** blocker and free radical scavenger, attenuates myocardial ischemia-reperfusion injury in hypercholesterolemic rabbits
AU Ma, Xin-Liang; Yue, Tian-Li; Lopez, Bernard L.; Barone, Frank C.; Christopher, Theodore A.; Ruffolo, Robert R., Jr.; Feuerstein, Giora Z.
CS Division Emergency Medicine, Thomas Jefferson Univ., Philadelphia, PA, USA
SO J. Pharmacol. Exp. Ther. (1996), 277(1), 128-36
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB Oxygen-derived free radicals play a crit. role in atherogenesis and reperfusion injury. The present expt. evaluated the effects of carvedilol, a new beta **adrenoreceptor** blocker with potent free radical-scavenging activity, on myocardial ischemia and reperfusion injury in a hypercholesterolemic rabbit model. New Zealand rabbits were fed a normal diet, a high-cholesterol diet, or a high-cholesterol diet supplemented with 1200 ppm carvedilol or propranolol. Eight weeks later, the rabbits were subjected to 60 min of myocardial ischemia followed by 60 min of reperfusion. The non-treated cholesterol-fed animals experienced greater cardiac damage after ischemia and reperfusion than rabbits fed a normal diet (necrosis 51% vs. 28% in the normal-diet group). In addn., non-treated cholesterol-fed rabbits showed a significantly decreased vasorelaxant response to ACh in U-46619-precontracted aortic rings (56% vs. 90% in the control group). Treatment with propranolol neither preserved endothelial function after cholesterol feeding nor reduced neutrophil accumulation in ischemic-reperfused myocardial tissue. Propranolol treatment did significantly decrease HR, pressure-rate index and infarct size (necrosis 33%). Despite their having essentially identical effects on HR and pressure-rate index, carvedilol exerted more profound cardiac protective effects than propranolol (necrosis 19%). Moreover, carvedilol treatment significantly preserved aortic endothelial function and markedly reduced neutrophil accumulation in ischemic-reperfused myocardial tissue. These results indicate that in addn. to its beta blocking activity, the antioxidant and endothelial protective activities of carvedilol contributed significantly to its cardiac protective effects after ischemia and reperfusion.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(carvedilol, a new beta **adrenoreceptor** blocker and free radical scavenger, attenuates **myocardial** ischemia-reperfusion injury in hypercholesterolemic rabbits)

L10 ANSWER 34 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1995:964214 HCAPLUS
DN 124:75193
TI Carvedilol update III: rationale for use in congestive heart failure
AU Feuerstein, Giora Z.; Poste, George; Ruffolo, Robert R.
CS SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406-0939, USA
SO Drugs Today (1995), Volume Date 1995, 31(Suppl. F), 1-23
CODEN: MDACAP; ISSN: 0025-7656
DT Journal; General Review
LA English
AB A review with 103 refs. In Feb. of 1995, several multicenter, double-blind, placebo-controlled clin. trials of the novel, multiple action cardiovascular drug, carvedilol, were terminated prematurely for ethical reasons due to the remarkable redn. in mortality obsd. in patients receiving carvedilol plus conventional therapy (i.e., angiotensin converting enzyme inhibitors, diuretics and digitalis) compared to patients receiving placebo plus conventional therapy. The dramatic redn. in mortality produced by carvedilol occurred across all studies and was obsd. in patients with mild, moderate and severe heart failure. The results of these dramatic clin. trials with carvedilol will be presented later this year. The purpose of this update is to describe in detail the multiple pharmacol. actions of carvedilol that make this drug unique, and which provide the rationale for its use in congestive heart failure. Carvedilol is both a .beta.-blocker and a vasodilator, and these activities produce significant redns. in myocardial work and reduce all three parameters of myocardial oxygen demand, namely heart rate, contractility and wall tension. The vasodilatory effects of carvedilol reduce afterload, and the resulting decrease in impedance to left ventricular ejection offsets the neg. inotropic effect resulting from .beta.-blockade, and as a result, stroke vol. and cardiac output are maintained or even increased in patients with congestive heart failure. Carvedilol and several of its metabolites are extremely potent antioxidants, and this activity may account for the dramatic cardioprotective effects obsd. in animal models, and may also protect the myocardium of patients with congestive heart failure where oxidative stress is now recognized to occur. The antioxidant effects of carvedilol may inhibit both the direct cytotoxic actions of reactive oxygen radicals as well as preventing oxygen radical-induced activation of transcription factors and genes assocd. with inflammatory processes and cardiac remodeling. Accordingly, carvedilol inhibits the gene expression of ICAM-1, a crit. adhesion mol. for polymorphonuclear leukocytes which typically infiltrate the myocardium under conditions of ischemia and exacerbate ischemic injury. These unique actions of carvedilol are not shared by any other drugs currently used in the management of congestive heart failure, or by any other .beta.-blockers. The multiple.
IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol update III: rationale for use in congestive **heart** failure)

L10 ANSWER 35 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1995:828151 HCAPLUS
DN 123:246460
TI Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure

AU Krum, Henry; Sackner-Bernstein, Jonathan D.; Goldsmith, Rochelle L.; Kukin, Marrick L.; Schwartz, Brian; Penn, Joshua; Medina, Norma; Yushak, Madeline; Horn, Evelyn; et al.
CS Cent. Heart Failure Res., Columbia Univ., New York, NY, USA
SO Circulation (1995), 92(6), 1499-506
CODEN: CIRCAZ; ISSN: 0009-7322
DT Journal
LA English
AB Clin. trials have shown that .beta.-adrenergic blocking drugs are effective and well tolerated in patients with mild to moderate heart failure, but the utility and safety of these drugs in patients with advanced disease have not been evaluated. We enrolled 56 patients with severe chronic heart failure into a double-blind, placebo-controlled study of the vasodilating .beta.-blocker carvedilol. All patients had advanced heart failure, as evidence by a mean left ventricular ejection fraction of 0.16 .+-. 0.01 and a mean maximal oxygen consumption of 13.6 .+-. 0.6 mL.cntdot.kg-1.cntdot.min-1 despite digitalis, diuretics, and an angiotensin-converting enzyme inhibitor (if tolerated). After a 3-wk, open-label, up-titrn. period, 49 of the 56 patients were assigned (in a double-blind fashion using a 2:1 randomization) to receive either carvedilol (25 mg BID, n = 33) or matching placebo (n = 16) for 14 wk, while background therapy remained const. Hemodynamic and functional variables were measured at the start and end of the study. Compared with the placebo group, patients in the carvedilol group showed improved cardiac performance, as reflected by an increase in left ventricular ejection fraction (P = .005) and stroke vol. index (P = .010) and a decrease in pulmonary wedge pressure, mean right atrial pressure, and systemic vascular resistance (P = .003, .002, and .017, resp.). In addn., compared with placebo, patients treated with carvedilol benefited clin., as shown by an improvement in symptom scores (P = .002), functional class (P = .013), and submaximal exercise tolerance (P = .006). The combined risk of death, worsening heart failure, and life-threatening ventricular tachyarrhythmia was lower in the carvedilol group than in the placebo group (P = .028), but carvedilol-treated patients had more dizziness and advanced heart block. Carvedilol produces clin. and hemodynamic improvement in patients who have severe heart failure despite treatment with angiotensin-converting enzyme inhibitors.
IT **72956-09-3**, Carvedilol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(double-blind, placebo-controlled study of the long-term efficacy of carvedilol in humans with severe chronic **heart** failure)

L10 ANSWER 36 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1995:736712 HCAPLUS
DN 123:131834
TI Carvedilol, a novel multiple action antihypertensive agent with antioxidant activity and the potential for myocardial and vascular protection
AU Feuerstein, G. Z.; Ruffolo, R. R.
CS Division Pharmacological Sciences, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SO Eur. Heart J. (1995), 16(Suppl. F), 38-42
CODEN: EHJODF; ISSN: 0195-668X
DT Journal; General Review
LA English
AB A review with 21 refs. Carvedilol is a vasodilating, .beta.-**adrenoceptor antagonist** currently marketed for the treatment of mild to moderate hypertension. Carvedilol acts to

reduce total peripheral resistance by blocking peripheral vascular .alpha.1-**adrenoceptors**, thereby producing systemic arterial vasodilation, while at the same time inhibiting reflex tachycardia through the blockade of myocardial .beta.-**adrenoceptors**. In addn. to its established efficacy and safety as an antihypertensive agent, carvedilol has been shown to produce significant cardioprotection in exptl. animal models of acute myocardial infarction, with the most dramatic effect being obsd. in the pig model of myocardial ischemia and reperfusion, where the redn. in infarct size reached 91%. Recent pharmacol. studies have revealed addnl. novel properties of carvedilol which may account for the marked protection produced by the drug in the ischemic myocardium and which may also result in protection against other chronic pathol. processes, such as atherosclerosis and acute vascular injuries. The latter arise from surgical procedures, such as percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. Specifically, carvedilol, as well as some of its hydroxylated metabolites, are potent antioxidants. In physicochem., biochem. and cellular assays, carvedilol and several of its metabolites prevent lipid peroxidn. and the depletion of endogenous antioxidants, such as vitamin E and glutathione. Moreover, carvedilol and its metabolites prevent the oxidn. of LDL to oxidized LDL, the latter being directly cytotoxic and known to activate monocytes/macrophages and to stimulate foam cell formation. In addn., carvedilol was found to inhibit both rat and human vascular smooth muscle cell proliferation and migration. The ability of carvedilol to inhibit vascular smooth muscle proliferation was obsd. against a wide variety of mitogens (e.g., PDGF, FGF, ET-1, thrombin, serum), indicating that the site of inhibition is likely to be through some final common pathway beyond the specific mitogen **receptors**. Likewise, carvedilol inhibited vascular smooth muscle cell migration to multiple chemoattractants, including PDGF and osteopontin. The significance of these activities of carvedilol to inhibit vascular smooth muscle cell migration and proliferation, which have been demonstrated in vitro, were also investigated in vivo in a rat model of neointima formation following acute carotid artery injury by balloon angioplasty. In this model, carvedilol inhibited, by 85%, the growth of neointima resulting from the vascular injury, and did so at a dosage that is similar to that used in humans for the treatment of angina. Taken together, these results indicate that carvedilol is a unique multiple action antihypertensive drug which not only normalizes blood pressure, but may also provide protection for the major organs of the cardiovascular system, and in particular the heart and vasculature.

IT **72956-09-3**, Carvedilol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carvedilol antihypertensive and antioxidant activity and potential for **myocardial** and vascular protection)

L10 ANSWER 37 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1995:736711 HCAPLUS
DN 123:132492
TI Vasodilating beta-blockers in heart failure
AU Raftery, E. B.
CS MRC Division Cardiovascular Diseases, Northwick Park Hospital Clinical Research Center, Harrow, UK
SO Eur. Heart J. (1995), 16(Suppl. F), 32-7
CODEN: EHJODF; ISSN: 0195-668X
DT Journal
LA English
AB Carvedilol is a nonselective .beta.-**adrenoceptor**

antagonist with vasodilating properties which has been shown to be effective in the management both of hypertension and of stable angina pectoris. In order to explore its wider efficacy in patients with manifest heart failure, a preliminary study was performed in patients with chronic stable angina pectoris accompanied by abnormal left ventricular wall motion, but without over heart failure (mean ejection fraction <40%). Six patients were given carvedilol 25 mg b.i.d. for 2 wk followed by 50 mg b.i.d. for a further 2 wk according to a single-blind placebo-controlled protocol. At the end of the 4 wk period of treatment, in four patients left ventricular wall motion was improved, in two it was unchanged, and in none was there any deterioration; mean ejection fraction increased from 40 to 48%. These results prompted a further study in 17 patients with chronic ischemic heart failure. The hemodynamic and clin. responses to i.v. carvedilol followed by the oral drug (50 mg b.i.d.) for 8 wk were studied. There was an improvement in all hemodynamic variables, although postural hypotension necessitated withdrawing two patients, and clin. deterioration was evident in two others. The beneficial effects of carvedilol were considered to be related to the combined redn. in afterload and inhibition of neurohumeral activation. There results have been confirmed in placebo-controlled, double-blind studies.

IT **72956-09-3**, Carvedilol
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(vasodilating beta-blockers in **heart** failure)

L10 ANSWER 38 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1995:579180 HCAPLUS
DN 122:306224
TI Antiarrhythmic effects of carvedilol in rat isolated heart subjected to regional ischemia and reperfusion
AU Bril, Antoine; Tomasi, Valerie; Laville, Marie-Paule
CS Unite de Recherche, SmithKline Beecham Laboratoires Pharmaceutiques, Saint-Gregoire, 35760, Fr.
SO Pharmacol. Commun. (1995), 5(4), 291-300
CODEN: PCMME9; ISSN: 1060-4456
DT Journal
LA English
AB The antiarrhythmic effect of carvedilol, a novel .beta.-**adrenoceptor antagonist** with vasodilating properties was assessed in rat isolated heart. Langendorff perfused rat hearts were subjected to regional myocardial ischemia, induced by ligation of the left main coronary artery, followed by a reperfusion period. Administered at increasing concns. (0.01, 0.1 and 1.0 .mu.M) carvedilol did not change coronary flow and heart rate during the preischemic and ischemic periods. During the reperfusion, heart rate wa slightly reduced by the high concn. of carvedilol (1.0 .mu.M) without any other hemodynamic alteration. A high incidence of ventricular tachycardia and ventricular fibrillation (92-100%) occurred at the time of reperfusion in hearts perfused with normal soln. or in presence of the vehicle. Carvedilol reduced the incidence of these severe ventricular arrhythmias esp. at the highest concn. (1.0 .mu.M) since none of the hearts presented any episode of ventricular tachycardia or ventricular fibrillation. Moreover, even at lower concn. carvedilol was able to decrease the duration of reperfusion-induced ventricular arrhythmias. These results obtained in an isolated heart prepn. suggest that carvedilol may exhibit antiarrhythmic effect by direct cardiac protective mechanism.

IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiarrhythmic effect of carvedilol in **heart** subjected

to regional ischemia and reperfusion)

L10 ANSWER 39 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1994:671726 HCAPLUS
DN 121:271726
TI Comparison of the ability of two vasodilating .beta.-blockers, carvedilol and celiprolol, to reduce infarct size in a pig model of acute myocardial infarction
AU Feuerstein, G. Z.; Ruffolo, R. R., Jr.
CS Dep. Cardiovascular Pharmacol., SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SO Pharmacol. Commun. (1994), 5(1), 57-63
CODEN: PCMME9; ISSN: 1060-4456
DT Journal
LA English
AB The cardioprotective actions of two vasodilating .beta.-**adrenoceptor** blocking agents were studied in a pig model of acute myocardial infarction induced by ischemia (45 min) followed by reperfusion (4 h). Carvedilol (1 mg/kg, i.v., 15 min pre-ischemia, n = 6) reduced infarct size by 90%, whereas celiprolol (3 mg/kg, 10 mg/kg or 10 mg/kg .times. 2, n = 5, 15 min pre-ischemia) failed to reduce infarct size. The results indicate that significant differences exist between these two vasodilating .beta.-adrenergic blocking agents with respect to their ability to produce cardioprotection. Carvedilol, which reduces peripheral vascular resistance primarily by blocking .alpha.1-**adrenoceptors**, provides marked cardioprotection, whereas celiprolol, which produces vasodilation via .beta.2-**adrenoceptor** stimulation, is devoid of cardioprotective actions. It is concluded therefore, that the cardioprotection commonly assocd. with .beta.-blockers may not be a universal feature of all of the new generation of vasodilating .beta.-blockers, but rather may be assocd. with some members of this class, such as carvedilol, but not with others, such as celiprolol.
IT **72956-09-3**, Carvedilol
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vasodilators carvedilol vs. celiprolol redn. of **myocardial infarction**)

L10 ANSWER 40 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1994:208215 HCAPLUS
DN 120:208215
TI Cardioprotective potential of carvedilol
AU Ruffolo, Robert R. Jr.; Bril, Antoine; Feuerstein, Giora Z.
CS Dep. Pharmacol., SmithKline Beecham Pharm. p.l.c., King of Prussia, PA, 19406, USA
SO Cardiology (1993), 82(Suppl. 3), 24-8
CODEN: CAGYAO; ISSN: 0008-6312
DT Journal
LA English
AB Carvedilol is a multiple-action cardiovascular agent that is a nonselective .beta.-**adrenoceptor antagonist** and a vasodilator. .beta.-**Adrenoceptor antagonists** reduce myocardial work, secondary to redns. in heart rate and contractility, both in animals and in humans. For these reasons, carvedilol may improve survival of acutely ischemic myocardium. The addnl. vasodilating activity of carvedilol, further reducing myocardial work by decreasing afterload and ventricular wall tension, may provide addnl. salvage over that afforded by .beta.-**adrenoceptor** blockade alone. The comparative ability of carvedilol and propranolol to reduce infarct size in exptl. models of acute myocardial infarction in the rat, pig and dog has been investigated utilizing a variety of exptl. techniques. In the pig, the calcium channel **antagonist**, diltiazem, was also

included as a second comparator agent. Infarct size was examd. on stained tissue sections using quant. image anal. In the rat, carvedilol (1 mg/kg) reduced infarct size by 47% ($p < 0.01$, $n = 11$), and in the pig, carvedilol, at doses of 0.3 and 1 mg/kg, reduced infarct size by 46% ($p < 0.05$, $n = 6$) and 89% ($p < 0.001$, $n = 6$), resp. In dogs subjected to ischemia and reperfusion, carvedilol (1 mg/kg) reduced infarct size by 78% ($p < 0.02$, $n = 6$), and in dogs subjected to permanent left anterior descending coronary artery occlusion, carvedilol, at doses of 0.3 and 1 mg/kg, reduced infarct size by 46 and 63%, resp. ($p < 0.02$, $n = 12-16$). In all studies, the extent of myocardial survival on carvedilol exceeded that on propranolol. In the pig, the redn. in infarct size produced by carvedilol exceeded that provided by diltiazem. Taken together, these studies demonstrate the ability of carvedilol to protect ischemic myocardial tissue from necrosis.

IT **72956-09-3**, Carvedilol
RL: BIOL (Biological study)
(**myocardial infarction** response to, propranolol and diltiazem comparison with)

L10 ANSWER 41 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1994:95245 HCAPLUS
DN 120:95245
TI Carvedilol, a new vasodilator and .beta.-**adrenoceptor antagonist**, inhibits oxygen-radical-mediated lipid peroxidation in swine ventricular membranes
AU Yue, Tian Li; Liu, Tane; Feuerstein, Giora
CS Dep. Pharmacol., SmithKline Beecham Pharm., King of Prussia, PA, 19406-0939, USA
SO Pharmacol. Commun. (1992), 1(1), 27-35
CODEN: PCMME9; ISSN: 1060-4456
DT Journal
LA English
AB The effect of carvedilol on free-radical-initiated lipid peroxidn. (LPO) in swine ventricular membranes was studied and compared with that of 3 other .beta.-blockers and the lazaroid U74500A. Fe2+-vitamin C and dihydroxyfumurate (DHF)/Fe3+-ADP induced a time-dependent LPO measured as thiobarbituric acid-reactive substance (TBARS). Carvedilol rapidly inhibited Fe2+-vitamin C- and DHF/Fe3+-ADP-initiated TBARS formation in a concn.-dependent manner, with IC50 values of 5.1 .mu.M and 14 .mu.M, resp. Under the same conditions, the IC50 values for inhibition of Fe2+-vitamin C- and DHF/Fe3+-ADP-induced LPO were 1.3 and 4.1 mM, resp., for pindolol, 0.9 and 2.2 mM, resp., for atenolol, and 4.6 and 3.5 .mu.M, resp., for U74500A. Propranolol had a mild inhibitory action only on DHF/Fe3+-ADP-induced LPO, with an IC50 value of 3.8 mM. In view of the pathol. importance of LPO in cardiac ischemic injury, inhibition of LPO may underlie the myocardial-protective activity of carvedilol and reinforce its potential beneficial effect in the treatment of ischemic heart disease.
IT **72956-09-3**, Carvedilol **95093-99-5**, R-(+)-Carvedilol **95094-00-1**, S-(-)-Carvedilol
RL: BIOL (Biological study)
(lipids peroxidn. mediated by oxygen radicals inhibition by, **heart** ischemic injury treatment in relation to)

L10 ANSWER 42 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1993:573863 HCAPLUS
DN 119:173863
TI Myocardial protection by the novel vasodilating beta-blocker, carvedilol: potential relevance of antioxidant activity
AU Feuerstein, Giora Z.; Yue, Tian Li; Cheng, Hung Yuan; Ruffolo, Robert R., Jr.
CS Dep. Pharmacol., SmithKline Beecham Pharm., King of Prussia, PA,

19406-0930, USA
SO J. Hypertens. (1993), 11(Suppl. 4), 541-548
CODEN: JOHYD3; ISSN: 0263-6352
DT Journal
LA English
AB Because O radicals are believed to influence ischemic tissue injuries, a study was designed to det. whether carvedilol has antioxidant actions which could contribute its cardioprotective properties. Four different models of acute myocardial infarction were examd. in 3 animal species, and the effects of carvedilol were compared to those of propranolol. First, in rats subjected to 30 min of cardiac ischemia followed by 24 h of reperfusion, carvedilol was administered both pre- and post-ischemia (1 mg/kg, i.v.). Second, minipigs were subjected to 45 min of cardiac ischemia followed by 4 h of reperfusion, with carvedilol pretreatment (0.3 or 1 mg/kg i.v.). Third, dogs were subjected to 1 h of cardiac ischemia followed by 24 h of reperfusion with carvedilol pretreatment (1 mg/kg, i.v.) or to permanent coronary occlusion (6 h) with carvedilol pretreatment (0.3 or 1 mg/kg, i.v.). Finally, to examine the antioxidant activity of carvedilol, pig myocardial membranes were exposed to oxidizing systems that elicit lipid peroxide products assessed as thiobarbituric acid-reactive substances (TBARS). In the rats, carvedilol reduced the infarct size by 47%, in contrast to propranolol, which is inactive in this model. In the minipigs the infarct size was reduced by 46 and 89% with carvedilol at 0.3 and 1 mg/kg, resp,; at comparable .beta.-**adrenoceptor** blocking doses, carvedilol produced a greater redn. in the infarct size than propranolol (89 vs. 48%). In dogs, carvedilol reduced the infarct size by 78% compared to the 64% redn. produced by propranolol. In dogs, with permanent coronary occlusion, carvedilol produced dose-dependent redns. in the infarct size of 46 and 63% for 0.3 and 1 mg/kg, resp., compared to propranolol which did not reduce the infarct size in this model. Carvedilol inhibited lipid peroxidn. in a dose-dependent manner with a 50% inhibitory concn. (IC50) of 5 .mu.mol/L. Moreover, superoxide generation by activated human neutrophils in vitro was also inhabited by carvedilol with an IC50 of 28 .mu.mol/L. Finally, carvedilol was shown to scavenge O free radicals in a cell-free system with an IC50 of 25 .mu.mol/L. These data indicate that carvedilol is a potent cardioprotective drug, which presumably acts by multiple mechanisms, possibly including a novel antioxidant effect that is not shared by other .beta.-blockers.
IT **72956-09-3**
RL: BIOL (Biological study)
(**myocardial** protection by, antioxidant activity in)

L10 ANSWER 43 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1993:400101 HCAPLUS
DN 119:101
TI Carvedilol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy
AU McTavish, Donna; Campoli-Richards, Deborah; Sorkin, Eugene M.
CS Adis Intl. Ltd., Auckland, N. Z.
SO Drugs (1993), 45(2), 232-58
CODEN: DRUGAY; ISSN: 0012-6667
DT Journal; General Review
LA English
AB A review with .apprx.120 refs. Carvedilol is a .beta.-**adrenoceptor antagonist** which also causes peripheral vasodilation primarily via .alpha.1-adrenergic blockade. Carvedilol produces its antihypertensive effects partly by reducing the total peripheral resistance by blocking .alpha.1-**adrenoceptors** and by preventing .beta.-**adrenoceptor** -mediated compensatory mechanisms. This combined action avoids many

of the unwanted effects assocd. with traditional .beta.-blocker or vasodilator therapy. In clincial trials, the antihypertensive efficacy of carvedilol administered once daily was similar to that of atenolol, labetalol, pindolol, propranolol, metoprolol, nitrendipine (in elderly patients), slow release nifedipine, or captopril in patients with mild-to-moderate essential hypertension. Combined therapy with carvedilol 25 mg and hydrochlorothiazide 25 mg, nicardipine 60 mg, or slow release nifedipine 20 mg had an additive antihypertensive effect. Carvedilol and atenolol at similar doses were equally effective at reducing blood pressure in patients who had not responded adequately to hydrochlorothiazide monotherapy. In patients with diabetes mellitus, carvedilol does not affect glucose tolerance or carbohydrate metab. Carvedilol and slow release nifedipine have similar efficacy in patients with stable angina pectoris. Carvedilol has a beneficial hemodynamic effect in patients with congestive heart failure secondary to ischemic heart disease. Carvedilol is generally well tolerated, with only 7% of patients withdrawing from treatment because of adverse events. Vertigo, headache, bronchospasm, fatigue, and skin reactions were the most common events causing drug withdrawal. Thus, carvedilol is a valuable drug for treating patients with mild-to-moderate essential hypertension and may offer particular benefits in specific populations of hypertensive patients.

IT **72956-09-3**, Carvedilol
RL: BIOL (Biological study)
(**cardiovascular** pharmacol. of, in humans)

L10 ANSWER 44 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1993:225304 HCAPLUS
DN 118:225304
TI Norepinephrine-induced changes in rat heart function, metabolism, and weight are **antagonized** by carvedilol
AU Nagano, T.; O'Harrow, S.; Sponer, G.; Zimmer, H. G.
CS Dep. Physiol., Univ. Munich, Munich, 8000/2, Germany
SO J. Cardiovasc. Pharmacol. (1993), 21(4), 530-6
CODEN: JCPCDT; ISSN: 0160-2446
DT Journal
LA English
AB One aim of this study was to characterize in intact rats the pharmacol. effects of carvedilol. After 3 days of continuous i.v. infusion of carvedilol (0.5 mg/kg/h), the pos. chronotropic and inotropic effects of i.v. bolus injections of isoproterenol (0.1, 0.3, and 1 .mu.g/kg) and phenylephrine (3, 10, and 30 .mu.g/kg), resp., were measured and compared with those obtained in rats that received a continuous i.v. infusion of 0.9% NaCl, prazosin (0.1 mg/kg/h), and propranolol (0.5 mg/kg/h). The chronotropic response to isoproterenol was less blunted in carvedilol-treated animals than in propranolol-treated animals. The pressure response to phenylephrine was attenuated only moderately. Thus, carvedilol had .beta.-**receptor** blocking actions on intact rat heart that were similar to but not as pronounced as those of propranolol. Because it reduced diastolic aortic pressure (DAP) and left ventricular systolic pressure (LVSP), it also had a moderate vasodilating effect. Carvedilol (continuous i.v. infusion of 0.25 and 0.5 mg/kg/h) **antagonized** the effects of norepinephrine (NE, i.v. infusion of 0.2 mg/kg/h for 3 days) on heart function and heart wt. in a dose-dependent manner. It also attenuated markedly the norepinephrine (NE)-induced increase in the activity of cardiac glucose 6-phosphate dehydrogenase (G-6-PD), the first and rate-limiting enzyme of the oxidative pentose phosphate pathway (PPP), although a 37% stimulation persisted.

IT **72956-09-3**, Carvedilol
RL: BIOL (Biological study)
(norepinephrine-induced changes in **heart** function and

metab. and wt. **antagonism** by)

L10 ANSWER 45 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1993:139222 HCAPLUS
DN 118:139222
TI Carvedilol, a new vasodilator and beta **adrenoceptor antagonist**, is an antioxidant and free radical scavenger
AU Yue, Tian Li; Cheng, Hung Yuan; Lysko, Paul G.; McKenna, Patrick J.; Feuerstein, Ron; Gu, Juan Li; Lysko, Kathryn A.; Davis, Louisa L.; Feuerstein, Giora
CS Div. Pharamcol., SmithKline Beecham Pharm., King of Prussia, PA, USA
SO J. Pharmacol. Exp. Ther. (1992), 263(1), 92-8
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB The antioxidant effect of carvedilol, a new vasodilating, .beta.-**adrenoceptor** blocker was studied and compared with five other .beta.-blockers. Carvedilol rapidly inhibited Fe++-initiated lipid peroxidn., measured as thiobarbituric acid reactive substance (TBARS), in rat brain homogenate with an IC50 of 8.1 .mu.M. Under the same conditions, the IC50 values of atenolol, pindolol, propranolol, celiprolol and labetalol were over 1.0 mM. Carvedilol protected against Fe++-induced .alpha.-tocopherol depletion in rat brain homogenate with an IC50 of 17.6 .mu.M; propranolol, celiprolol and labetalol, up to 200 .mu.M, did not show any effect. Using dihydroxyfumarate/Fe++-ADP as a OH.cntdot. radical generating system and 5,5-di-Me pyrroline-N-oxide (DMPO) as a trapping agent, the characteristic DMPO-OH signals were monitored by ESR. Carvedilol dose-dependently decreased the intensity of the DMPO-OH signal, with an IC50 of 25 .mu.M, whereas propranolol, at 500 .mu.M, and U74500A, a 21-aminosteroid, at 100 .mu.M, had no effect. The antioxidant effect of carvedilol mainly resides in the carbazole moiety, and the substitution of a hydroxyl group at certain positions on the Ph ring of either carbazole or the ortho-substituted phenoxylethyllamine part of carvedilol resulted in an increase in antioxidant activity. Futhermore, the protective effect of carvedilol analogs against OH.cntdot.-mediated neuronal death pos. correlated to their antioxidant effect. Thus, carvedilol is a far more potent antioxidant than other commonly used .beta.-blockers. The apparent mechanism of carvedilol's inhibition of lipid peroxidn. is mainly via scavenging free radicals. This novel property of carvedilol may contribute to the known cardioprotective activity of this compd.
IT **72956-09-3**, Carvedilol **95093-99-5**, R-(+)-Carvedilol **95094-00-1**, S-(-)-Carvedilol
RL: BIOL (Biological study)
(antioxidant and free radical scavenging activity of, **cardioprotectant** effects in relation to)

L10 ANSWER 46 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1992:503877 HCAPLUS
DN 117:103877
TI Cardioprotective effects of carvedilol, a novel .beta. **adrenoceptor antagonist** with vasodilating properties, in anesthetized minipigs: comparison with propranolol
AU Bril, Antoine; Slivjak, Mark; DiMartino, Michael J.; Feuerstein, Giora Z.; Linee, Phillippe; Poyser, Robert H.; Ruffolo, Robert R., Jr.; Smith, Edward F., III
CS Dep. Pharmacol., SmithKline Beecham Pharm. PLC, King of Prussia, PA, 19406, USA
SO Cardiovasc. Res. (1992), 26(5), 518-25
CODEN: CVREAU; ISSN: 0008-6363
DT Journal
LA English
AB The aim was to evaluate in a minipig model of acute myocardial

infarction the cardioprotection provided by the .beta. **adrenoceptor** blocking and vasodilating activities present in carvedilol; comparison was made to the pure .beta. **adrenoceptor antagonist**, propranolol. Expts. were performed in 25 Yucatan minipigs (9-12 kg), randomly assigned to receive vehicle (n = 7), carvedilol 0.3 mg.kg-1 (n = 6), carvedilol 1 mg.kg-1 (n = 6), or propranolol 1 mg.kg-1 (n = 6). Myocardial infarction was produced by occlusion of the left anterior descending coronary artery for 45 min followed by 4 h of reperfusion. Vehicle, carvedilol (0.3 and 1 mg.kg-1) or propranolol (1 mg.kg-1) were given i.v. 15 min before the coronary artery occlusion. At the end of the reperfusion period, infarct size was detd. using Evans blue dye and triphenyltetrazolium chloride staining. Carvedilol (1 mg.kg-1) reduced infarct size by over 90% without producing pronounced changes in systemic hemodynamic variables. The ability of carvedilol to reduce infarct size was clearly dose dependent. Thus infarct size, which represented 27.5(SEM 2.3)% of the area at risk in the vehicle treated group, was only 13.1(4.0)% and 2.4(1.5)% in pigs treated with carvedilol at 0.3 and 1 mg.kg-1, resp. In animals treated with propranolol (1 mg.kg-1), infarct size represented 10.9(2.4)% of the area at risk. The 60% and 91% redns. in infarct size produced by propranolol (1 mg.kg-1) and carvedilol (1 mg.kg-1), resp., were clearly evident upon three dimensional image anal. The redn. in infarct size was significantly greater for carvedilol (1 mg.kg-1) compared to propranolol (1 mg.kg-1) at equiv. .beta. **adrenoceptor** blocking doses. Pretreatment with propranolol did not reduce the increases in myeloperoxidase activity obsd. in the area at risk or in the infarcted area. In contrast, carvedilol produced a dose dependent redn. in myeloperoxidase activity in these areas. Carvedilol limits myocardial necrosis resulting from coronary artery occlusion and reperfusion in a more pronounced manner than the pure .beta. **adrenoceptor antagonist**, propranolol. The cardioprotective effect of carvedilol, which reduced infarct size by 91%, may result from the combined effects of .beta. **adrenoceptor** blockade and vasodilatation, and possibly also from inhibition of intracellular calcium overload in cardiac cells resulting from **antagonism** of myocardial .alpha.1 **adrenoceptors** and/or calcium channel blockade. The cardioprotection provided by carvedilol may ultimately be of benefit in hypertensive patients who are at risk for acute myocardial infarction.

IT **72956-09-3**, Carvedilol
RL: PRP (Properties)
(**cardioprotective** effects of, in acute **myocardial infarction**)

L10 ANSWER 47 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1992:420266 HCAPLUS
DN 117:20266
TI Myocardial protection with carvedilol
AU Feuerstein, Giora Z.; Hamburger, Steven A.; Smith, Edward F., III; Bril, Antoine; Ruffolo, Robert R., Jr.
CS Dep. Pharmacol., SmithKline Beecham Pharm. PLC, King of Prussia, PA, USA
SO J. Cardiovasc. Pharmacol. (1992), 19(Suppl. 1), S138-S141
CODEN: JCPCDT; ISSN: 0160-2446
DT Journal
LA English
AB Carvedilol is a multiple-action cardiovascular agent that is both a .beta.-**adrenoceptor antagonist** and a vasodilator and has recently been made available for the treatment of mild-to-moderate hypertension. Clin. trials are ongoing to establish the efficacy of carvedilol in angina and congestive heart failure. .beta.-**Adrenoceptor antagonists** are

known to reduce myocardial work secondary to redns. in heart rate and contractility; accordingly, they have been shown to be cardioprotective in animals and in humans. Because carvedilol has .beta.-**adrenoceptor antagonist** activity, it also should provide significant cardioprotection. The addnl. vasodilating activity of carvedilol, which will further reduce myocardial work by decreasing afterload and myocardial wall tension, should provide more salvage of ischemic myocardium than that afforded by a pure .beta.-**adrenoceptor antagonist**, such as propranolol. The ability of carvedilol and propranolol to reduce infarct size was investigated in exptl. models of acute myocardial infarction in the rat, pig, and dog. The left anterior descending coronary artery was occluded for 30 (rat) or 45 min (pig) and then reperfused for 24 h (rat) or 4 h (pig). In the dog, the left circumflex coronary artery was occluded for 60 min and reperfused for 24 h. Vehicle, carvedilol, or propranolol was administered i.v. 15 min before ischemia (and, in the rat only, repeated 4 h after ischemia). An addnl. group of dogs was subjected to permanent left anterior descending coronary artery occlusion for 6 h, and carvedilol or propranolol was given 15 min after occlusion. Infarct size was examd. on stained tissue sections using quant. image anal. In the rat, carvedilol (1 mg/kg) reduced infarct size by 47%. In the pig, carvedilol reduced infarct size by 46% and 89% at doses of 0.3 and 1 mg/kg, resp. In dogs subjected to ischemia and reperfusion, carvedilol (1 mg/kg) reduced infarct size by 78%. In dogs subjected to permanent left anterior descending coronary artery occlusion, carvedilol reduced infarct size by 46% and 63% at doses of 0.3 and 1 mg/kg, resp. In all studies, the highly significant myocardial protective effects of carvedilol exceeded those of the pure .beta.-**adrenoceptor antagonist** proparanolol. Taken together, these studies clearly demonstrate the efficacy of carvedilol in protecting ischemic myocardial tissue from necrosis. This cardioprotective effect of carvedilol may ultimately be of benefit when the drug is used in the treatment of hypertension and may also underlie the use of carvedilol in the treatment of angina and congestive heart failure.

IT **72956-09-3**, Carvedilol
RL: BIOL (Biological study)
(**cardioprotection** by, in **myocardial infarction**)

L10 ANSWER 48 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1992:420264 HCAPLUS
DN 117:20264
TI **Receptor** pharmacology of carvedilol in the human heart
AU Bristow, Michael R.; Larrabee, Patti; Minobe, Wayne; Roden, Robert; Skerl, Lisa; Klein, Jana; Handwerger, David; Port, J. David; Mueller-Beckmann, B.
CS Med. Cent., Univ. Utah, Salt Lake City, UT, USA
SO J. Cardiovasc. Pharmacol. (1992), 19(Suppl. 1), S68-S80
CODEN: JCPCDT; ISSN: 0160-2446
DT Journal
LA English
AB The .beta.-blocker and vasodilator carvedilol was examd. in prepns. of human ventricular myocardium. Carvedilol is a high-affinity, slightly .beta.1-selective competitive .beta.-blocking agent, with a KD for .beta.1-**receptors** of approx. 4-5 nM and a selectivity of sixfold to 39-fold for .beta.1-**receptors** rather than .beta.2-**receptors**, depending on the method used to assess subtype potency. Carvedilol also is a potent .alpha.1-blocking agent, with a .beta.1:.alpha.1-blocking relative potency of 1.7-fold. In human lymphocytes contg. .beta.2-**receptors** and human myocardial membranes contg. both .beta.1- and .beta.2-**receptors**, carvedilol exhibited the

unique property of guanine nucleotide-modulatable binding. This is a property shared with bucindolol, another .beta.-blocker and vasodilator that is structurally similar to carvedilol. Despite the presence of guanine nucleotide-modulatable binding, no intrinsic activity of carvedilol was detected in prepns. of isolated human heart or in myocardial membranes.

IT **72956-09-3**, Carvedilol
RL: BIOL (Biological study)
(**heart** failure treatment by, adrenergic **receptor** specificity in)

L10 ANSWER 49 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1992:187811 HCAPLUS
DN 116:187811
TI Cardioprotective effects of the vasodilator/beta-**adrenoceptor** blocker, carvedilol, in two models of myocardial infarction in the rat
AU Smith, E. F. III; Griswold, D. E.; Hillegass, L. M.; Slivjak, M. J.; Davis, P. A.; DiMartino, M. J.
CS Dep. Pharmacol., SmithKline Beecham, King of Prussia, PA, 19406, USA
SO Pharmacology (1992), 44(6), 297-305
CODEN: PHMGBN; ISSN: 0031-7012
DT Journal
LA English
AB The purpose of this study was to evaluate the cardioprotective effects of carvedilol, a .beta.-adrenergic blocker and vasodilator, in two models of ischemic myocardial damage in the rat. Following coronary artery occlusion for 0.5 h and reperfusion for 24 h (MI/R group), left ventricular (LV) injury was detd. by planimetric anal. of triphenyltetrazolium chloride-stained tissue, and polymorphonuclear leukocyte infiltration was assessed by measuring myeloperoxidase (MPO) activity. In the vehicle-treated MI/R group, infarct size was 14.2 of the LV, and MPO activity was increased to 2.8 from 0.14 U/g tissue in the vehicle-treated sham-occluded group. Carvedilol (1 mg/kg i.v., 15 min prior to coronary artery occlusion and at 3.5 h following reperfusion) reduced myocardial infarct size to 7.5% of the LV (n = 14) and attenuated the increase in MPO activity to 1.4 U/g tissue. A lower dose of carvedilol (i.e. 0.3 mg/kg i.v.) did not limit myocardial infarct size or the increase in MPO activity. In a model of permanent coronary artery occlusion, 24-h survival was reduced from 85% in sham-occluded animals to 44% in the vehicle-treated MI group. In comparison to the vehicle-treated MI group, carvedilol (0.3 mg/kg i.v., 15 min prior to coronary artery occlusion and 1 mg/kg 4 h after occlusion) improved survival by 55%, whereas the same dose of propranolol had no significant effect on survival. These results indicate that carvedilol reduces myocardial ischemia/reperfusion injury, and significantly improves survival in a permanent coronary artery occlusion model of myocardial infarction.

IT **72956-09-3**, Carvedilol
RL: PRP (Properties)
(**cardioprotective** effects of, in **myocardial infarction**)

L10 ANSWER 50 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1991:598096 HCAPLUS
DN 115:198096
TI Carvedilol (Kredex) reduces infarct size in a canine model of acute myocardial infarction
AU Hamburger, Steven A.; Barone, Frank C.; Feuerstein, Giora Z.; Ruffolo, Robert R., Jr.
CS Dep. Pharmacol., SmithKline Beecham Pharm., King of Prussia, PA, 19406-0939, USA
SO Pharmacology (1991), 43(3), 113-20

CODEN: PHMGBN; ISSN: 0031-7012
DT Journal
LA English
AB Carvedilol (Kredex) is a multiple action, antihypertensive agent that may also prove to be useful in the treatment of angina and congestive heart failure. Carvedilol combines in one mol. both .beta.-**adrenoceptor** blocking and vasodilating activities. Inasmuch as .beta.-**adrenoceptor** blocking agents are known to be cardioprotective and thereby reduce infarct size, it is logical to assume that carvedilol, likewise, would possess this desirable activity. Furthermore, the addnl. vasodilating activity of carvedilol could contribute to further redns. in infarct size by reducing myocardial work (and therefore myocardial oxygen demand) through redns. in both afterload and myocardial wall tension. As such, the authors investigated the ability of carvedilol to reduce infarct size in a canine model of acute myocardial infarction. Carvedilol (1 mg/kg i.v.) or its vehicle, DMF, were administered 15 min before left circumflex coronary artery (LCX) occlusion. Following 1 h of LCX occlusion, dogs were reperfused through a crit. stenosis and then allowed to recover for 24 h. Carvedilol-treated animals exhibited a 78% redn. in infarct size compared to vehicle controls, such that the percentage of the left ventricle infarcted was reduced from 16.2% in control animals to 3.6% in animals treated with carvedilol. Stained tissue sections of the left ventricle were photographed, digitized and color-enhanced using an Image Anal. Computer System, and three-dimensional reconstruction of the left ventricle, including the infarcted areas, was performed. Individual color-enhanced planar sections of the left ventricle showed clearly that carvedilol dramatically reduced the area of infarction, and three-dimensional reconstruction of the left ventricle illustrated a striking redn. in the vol. of the infarcted area in carvedilol-treated dogs. These data demonstrate clearly that carvedilol can markedly reduce infarct size in a canine model of acute myocardial infarction. This cardioprotective effect may result in addn. clin. benefit in patients treated with carvedilol for hypertension, angina or congestive heart failure.
IT **72956-09-3**, Carvedilol
RL: BIOL (Biological study)
(**infarct** size redn. by, in acute **myocardial infarction** model)

L10 ANSWER 51 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1991:505718 HCAPLUS
DN 115:105718
TI Adrenaline in cardiovascular diseases - effect of .beta.-**adrenoceptor antagonists**
AU Dehner, R.; Ikeda, K.; Yamori, Y.; Grobecker, H.
CS Dep. Pharmacol., Univ. Regensburg, Regensburg, D-8400, Fed. Rep. Ger.
SO Z. Kardiol. (1990), 79(Suppl. 3), 79-88
CODEN: ZKRDAX; ISSN: 0300-5860
DT Journal
LA English
AB The study provides further evidence for a permissive role of adrenaline as a co-transmitter in the initiation and/or maintenance of hypertension. Adrenaline, reaching the circulation by bolus injection from the adrenal glands, is first taken up by the sympathetic nerve terminals and along with the endogenous transmitter noradrenaline, it is released into the synaptic cleft upon nerve stimulation. By stimulating presynaptically localized .beta.2-**adrenoceptors**, adrenaline is able to facilitate transmitter release, resulting in enhanced infusion of noradrenaline into the circulation, thereby elevating peripheral sympathetic tone. Blockade of this adrenaline-mediated pos.-feedback mechanism is

supposed to be one important mechanism of action of nonselective .beta.-**adrenoceptor antagonists**. In the case of carvedilol this effect is supported through vasodilation by addnl. blockade of vascular .alpha.-**adrenoceptors**.

IT **72956-09-3**
RL: BIOL (Biological study)
(**cardiovascular** diseases therapy with, adrenaline in relation to)

L10 ANSWER 52 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1990:624330 HCAPLUS
DN 113:224330
TI Phase I study of carvedilol (DQ-2466), a new .beta.-blocker. 1. The study with single oral administration
AU Ajima, Haruhiro; Ota, Norihiko; Igarashi, Shogo; Yamamura, Hideo
CS Dep. Cardiovasc. Intern. Med., Ohmori Red Cross Hosp., Tokyo, 143, Japan
SO Rinsho Yakuri (1990), 21(2), 391-400
CODEN: RIYADS; ISSN: 0388-1601
DT Journal
LA Japanese
AB Carvedilol (DQ-2466) is a new .beta.-**adrenoblocker** with vasodilating properties. The hemodynamics effects and toxicity of carvedilol after single oral administration was studied in healthy men treated with 20, 40, or 60 mg carvedilol. Both systolic and diastolic blood pressures at rest decreased from 2 h to 24 h after the administration of carvedilol at each dose level. Max. decreases of the systolic and diastolic blood pressures were achieved 3-4 h after administration. The changes of systolic blood pressure were 4.2, 14.6, 16.2, and 16.6% in placebo, 20, 40, and 60 mg groups, resp., 3 h after dosing. The changes of diastolic blood pressure were 0.5, 16.1, 13.3, and 18.8% in placebo, 20, 40, and 60 mg groups, resp., 4 h after dosing. There was no difference in the changes of heart rate at rest between carvedilol-treated and placebo group. The stroke index (si) and cardiac index (ci) detd. by echocardiog. were not affected in the 20 mg group. SI and CI slightly decreased in the 40 mg group and there was a tendency to decrease in the 60 mg group. The total peripheral vascular resistance decreased at 4 and 29 h after the 20-mg dose. The increase of systolic blood pressure during treadmill exercise was reduced dose-dependently in the carvedilol groups for 9 h after dosing. There were no abnormal lab. findings. No subjective adverse symptoms were reported in the placebo and the 20 mg group. At the higher doses, some subjects felt headaches, nausea, and dizziness. Thus, carvedilol maintains marked hypotensive effects up to 24 h after single oral administration of 20 mg. The max. daily dose should be <40 mg in multiple dosing.

IT **72956-09-3**, Carvedilol
RL: BIOL (Biological study)
(**cardiovascular** effects of single doses of, in humans)

L10 ANSWER 53 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1989:608919 HCAPLUS
DN 111:208919
TI Effects of carvedilol on left ventricular function and arrhythmias during repeated short-time myocardial ischemia in experimental pigs
AU Hoeher, Martin; Friedrich, M.; Sommer, T.; Marten, A.; Ehmer, B.; Hombach, V.; Hirche, H.
CS Dep. Physiol., Univ. Cologne, Cologne, Fed. Rep. Ger.
SO Z. Kardiol. (1989), 78(Suppl. 3), 7-15
CODEN: ZKRDAX; ISSN: 0300-5860
DT Journal
LA English
AB In pigs with exptl. myocardial ischemia, i.v. administration of 0.01

mg/kg carvedilol decreased the heart rate, dp/dt max, and the ejection fraction, induced only a slight decrease of systolic pressure, and increased the vascular resistance, indicating a .beta.-blocker effect without vasodilation. Only a higher dose of 0.1 mg/kg had a vasodilatory effect. During ischemia carvedilol had no effect on the time-course or the extent of systolic bulging of the ischemic myocardium, but the ischemia-induced decrease of left ventricular ejection fraction was diminished. Both during short-term ischemia, as well as during the 60-min-ischemia-period carvedilol reduced ventricular premature beats. During the 60-min-ischemia-period, activation delay measured from local d.c.-electrograms of the ischemic myocardium, as well as the occurrence of activation block were not altered by carvedilol, as was the incidence of ventricular fibrillation (69%). Apparently, at low dosages, the .beta.-blocking effect of carvedilol exceeds the vasodilating properties. This may also hold true in patients with cardiac failure; they are more sensitive to .beta.-blocking drugs. During ischemia carvedilol slightly reduces the ischemia-dependent decrease of global ventricular function and it has an antiarrhythmic effect. Therefore, it may be protective in patients with acute myocardial infarction.

IT **72956-09-3**, Carvedilol
RL: BIOL (Biological study)
(**heart** ischemia treatment with, mechanism of)

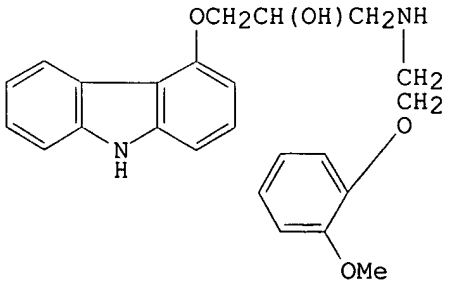
L10 ANSWER 54 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1989:490042 HCAPLUS
DN 111:90042
TI Interaction of selected vasodilating .beta.-blockers with adrenergic **receptors** in human cardiovascular tissues
AU Monopoli, A.; Forlani, A.; Bevilacqua, M.; Vago, T.; Norbiato, G.; Bertora, P.; Biglioli, P.; Alamanni, F.; Ongini, E.
CS Res. Lab., Essex Italia, Milan, I-20060, Italy
SO J. Cardiovasc. Pharmacol. (1989), 14(1), 114-20
CODEN: JCPCDT; ISSN: 0160-2446
DT Journal
LA English
AB .beta.- And .alpha.1-**adrenoceptor antagonist** properties of bufuralol, carvedilol, celiprolol, dilevalol, labetalol, and pindolol were investigated in human myocardium and mammary artery using binding techniques and functional studies. In myocardial membranes, .beta.-**adrenoceptor antagonists** showed monophasic competition isotherms for [125I]pindolol binding with high affinity (Ki from 1-100 nM), except for celiprolol which displayed a biphasic competition isotherm (pKi = 6.4 for .beta.1- and 4.8 for .beta.2-**adrenoceptors**). Drug interactions with .alpha.1-**adrenoceptors** were evaluated in human mammary artery by [3H]prazosin binding and by measuring contractile responses to norepinephrine (NE). Labetalol and carvedilol showed a moderate affinity for .alpha.1-**adrenoceptors** (pKi = 6.2 and 6.1, resp.), and inhibited NE-induced contractions (pA2 = 6.93 and 8.64, resp.). Dilevalol, bufuralol, and pindolol displayed weak effect both in binding (Ki in micromolar range) and functional expts. (pA2 = 5.98, 5.54, and 6.23, resp.). Celiprolol did not show **antagonist** properties up to 100 .mu.M in functional studies, but displayed a slight affinity for .alpha.1-**adrenoceptors** in binding studies. The data indicate that the vasodilating activity of these .beta.-**adrenoceptor antagonists** is caused by an .alpha.1-**adrenoceptor antagonism** (labetalol, carvedilol), whereas for the others alternative mechanisms should be considered.

IT **107741-96-8**
RL: BIOL (Biological study)
(adrenergic **receptors** in human **cardiovascular**

tissues response to, vasodilation in relation to)

L10 ANSWER 55 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1988:216064 HCAPLUS
DN 108:216064
TI Hemodynamics of carvedilol in normal subjects compared with propranolol, pindolol, and labetalol
AU Tomlinson, B.; Cronin, C. J.; Graham, B. R.; Prichard, B. N. C.
CS Middlesex Sch. Med., Univ. Coll., London, WC1E 6JJ, UK
SO J. Cardiovasc. Pharmacol. (1987), 10(Suppl. 11), S69-S75
CODEN: JCPCDT; ISSN: 0160-2446
DT Journal
LA English
AB Single doses, in log steps, of carvedilol from 12.5 to 200 mg, propranolol 40 to 320 mg, pindolol 2.5 to 20 mg, labetalol 50 to 400 mg, and placebo control were given randomized double blind to six healthy volunteers. Noninvasive measurements of blood pressure and heart rate were made supine, standing, and during cycle exercise 1 and 2 h postdose. All drugs produced a dose-dependent redn. in exercise heart rate, but this was greater for propranolol and pindolol than for carvedilol and labetalol at the doses studied. Exercise systolic blood pressure was similarly reduced but there was less sepn. in the dose response curves between the various drugs. Supine and standing heart rate was reduced only by propranolol, but supine systolic blood pressure was reduced by carvedilol (50, 100, and 200 mg), propranolol (40, 160, and 320 mg), pindolol (5, 10, and 20 mg), and labetalol (400 mg). Standing systolic blood pressure was reduced by carvedilol (50, 100, and 200 mg) and pindolol (2.5 and 20 mg). The effects of carvedilol on resting blood pressure suggest addnl. blood pressure lowering properties other than the pure .beta.-**antagonism** of propranolol. Effects on exercise heart rate and systolic blood pressure were similar to carvedilol (12.5-200 mg) with labetalol (50-400 mg), but changes in resting systolic blood pressure were less consistent with labetalol.
IT **72956-09-3**, Carvedilol
RL: PRP (Properties)
(**cardiovascular** effects of, in humans)

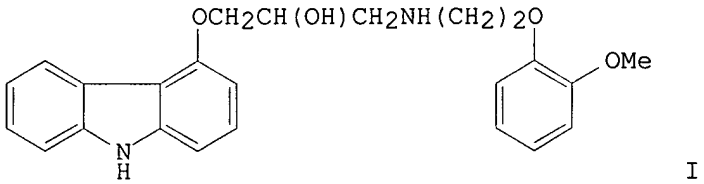
L10 ANSWER 56 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1987:207388 HCAPLUS
DN 106:207388
TI Pharmacological profile of carvedilol as a .beta.-blocking agent with vasodilating and hypotensive properties
AU Sponer, G.; Bartsch, W.; Strein, K.; Mueller-Beckmann, B.; Boehm, E.
CS Dep. Exp. Cardiovasc. Res., Boehringer Mannheim G.m.b.H., Mannheim, D-6800/31, Fed. Rep. Ger.
SO J. Cardiovasc. Pharmacol. (1987), 9(3), 317-27
CODEN: JCPCDT; ISSN: 0160-2446
DT Journal
LA English
GI



I

AB Carvedilol (I) [**72956-09-3**] is a new .beta.-**receptor**-blocking and vasodilating drug that is presently undergoing clin. trials in hypertension and coronary **heart** disease; the pharmacodynamic properties of carvedilol are compared with those of std. drugs. For the .beta.1-blockade in guinea pig atria, the pA10 (-log of concn. producing a 10%-inhibitory effect) values were 7.44 for carvedilol and 6.77 for propranolol. Carvedilol is a **noncardioselective** .beta.-blocker. The i.v. doses that inhibited the **tachycardia** by 50% induced by 1 .mu.g/kg isoprenaline were 62 .mu./kg in dogs, 138 .mu./kg in rabbits and 841 .mu.g/kg in rats. In rabbits carvedilol was slightly more active and in rats less active than propranolol. In all models, carvedilol was much more active than labetalol or prizidilol. In contrast to propranolol, carvedilol relaxed rat aortic strips. A dose-dependent decrease in arterial blood pressure was seen in different in vivo models. The total peripheral and coronary resistance were decreased in conscious dogs. The doses required for both .beta.-blockade and decrease in blood pressure were in the same range. The drug was also active after oral administration. There is no hint for development of tolerance.

L10 ANSWER 57 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1987:149153 HCAPLUS
DN 106:149153
TI Clinical pharmacology of carvedilol in normal volunteers
AU Cubeddu, Luigi X.; Fuenmayor, Nery; Varin, France; Villagra, Victor G.; Colindres, Romulo E.; Powell, J. Robert
CS DEp. Med., Univ. North Carolina, Chapel Hill, NC, 27514, USA
SO Clin. Pharmacol. Ther. (St. Louis) (1987), 41(1), 31-44
CODEN: CLPTAT; ISSN: 0009-9236
DT Journal
LA English
GI

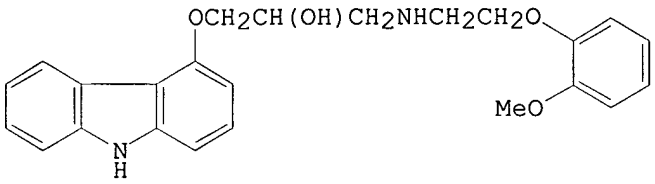


I

AB The mechanism of the vasodilatory action of carvedilol (BM 14190)(I) [**72956-09-3**], a new antihypertensive agent, was investigated in volunteers. Intraarterial blood pressure and ECG were monitored continuously. Carvedilol (1 mg/min for 15 min) produced a rapid redn. in blood pressure and a transient increase in **heart** rate. At the end of infusion, systolic and diastolic blood pressure were reduced by 23% and 18%, resp., whereas **heart** rate was not different from baseline. At the doses used, the hypotensive effect of carvedilol was greater than that of labetalol (36 and 72 mg in 15 min). Carvedilol and labetalol **antagonized** isoproterenol-induced hypotension and **tachycardia**, at serum levels .gtoreq.8 and 20 mg/mL, resp. Both drugs **antagonized** phenylephrine pressor effects. A similar degree of inhibition (25% of control) of pressor effects was obsd. for carvedilol and labetalol when their resp. serum concns. were 23 and 80 ng/mL. Neither carvedilol nor labetalol had any effect on AII (angiotensin II) pressor responses. Carvedilol serum

levels as high as 150 ng/mL failed to inhibit AII-induced pressor responses. Our results suggest that at the doses used in this study, carvedilol has both .alpha.1- and nonselective .beta.-**receptor** blocking properties. Moreover, carvedilol is .apprx.3-5 times more potent than labetalol in blocking .alpha.1- and .beta.-**receptors** and in reducing blood pressure.

L10 ANSWER 58 OF 58 HCAPLUS COPYRIGHT 1998 ACS
AN 1986:454343 HCAPLUS
DN 105:54343
TI Clinical pharmacologic investigations with carvedilol, a new beta-blocker with direct vasodilator activity
AU Von Moellendorff, Erika; Abshagen, Ulrich; Akpan, Waltraud; Neugebauer, Gunter; Schroeter, Eva
CS Clin. Pharmacol., Boehringer Mannheim G.m.b.H., Mannheim, D-6800/31, Fed. Rep. Ger.
SO Clin. Pharmacol. Ther. (St. Louis) (1986), 39(6), 677-82
CODEN: CLPTAT; ISSN: 0009-9236
DT Journal
LA English
GI



I

AB Carvedilol (BM 14.190)(I) [**72956-09-3**] was shown in healthy normotensive men to have .beta.-adrenergic blocking and vasodilating activity. By means of digital plethysmog., the threshold for vasodilation was ascertained at a dose of 2.6 mg i.v. infused over 1 h. The oral threshold dose was established at about 15 mg, with a linear increase in response (r = 0.78) up to 76.5 mg. This dose increased blood flow to the forearm by redn. of arterial resistance. Although venous capacity was not changed, postural symptoms in 3 subjects could also be indicative of venous involvement. Carvedilol, 50 mg, reduced exercise **heart** rate for about 10 h.

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               (72956-09-3/RN)
             1 95093-99-5/BI
               (95093-99-5/RN)
             1 95094-00-1/BI
               (95094-00-1/RN)
             1 107741-96-8/BI
               (107741-96-8/RN)
             1 146574-43-8/BI
               (146574-43-8/RN)
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L11  ANSWER 1 OF 4  REGISTRY  COPYRIGHT 1998 ACS
RN   146574-43-8  REGISTRY
CN   9H-Carbazol-3-ol, 4-[2-hydroxy-3-[[2-(2-
     methoxyphenoxy)ethyl]amino]propoxy]- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
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     methoxyphenoxy)ethyl]amino]propoxy]-, (.+-.)-
OTHER NAMES:
CN   BM 910228
CN   SB 211475
DR   154163-88-9
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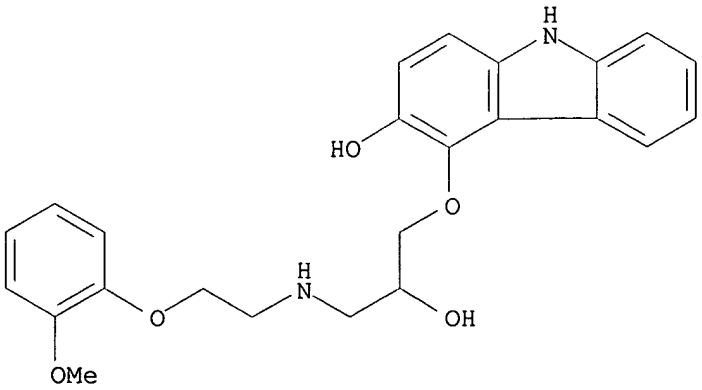


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REFERENCE 2: 126:166288

REFERENCE 3: 125:317250

REFERENCE 4: 118:139222

L11 ANSWER 2 OF 4 REGISTRY COPYRIGHT 1998 ACS
RN **95094-00-1** REGISTRY
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (-)-Carvedilol
CN (S)-(-)-Carvedilol
CN (S)-Carvedilol
FS STEREOSEARCH
MF C24 H26 N2 O4
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, DRUGPAT, DRUGUPDATES, IPA, TOXLINE, TOXLIT, USPATFULL
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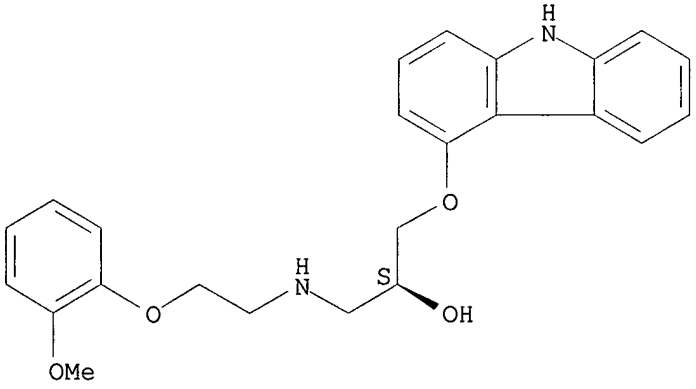

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REFERENCE 2: 128:18344

REFERENCE 3: 127:229175

REFERENCE 4: 127:199415

REFERENCE 5: 126:69750

REFERENCE 6: 125:184727

REFERENCE 7: 125:96309

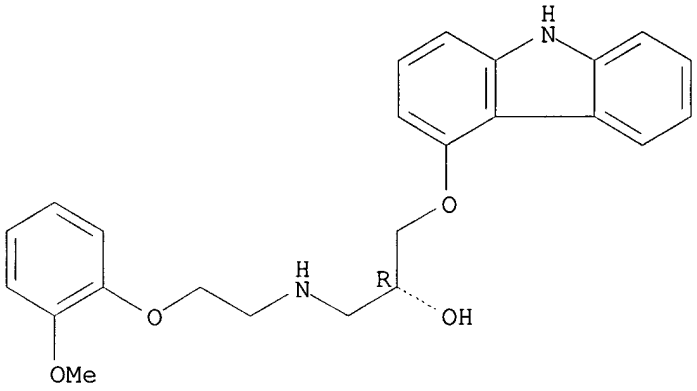
REFERENCE 8: 124:325510

REFERENCE 9: 123:101931

REFERENCE 10: 122:218

L11 ANSWER 3 OF 4 REGISTRY COPYRIGHT 1998 ACS
RN **95093-99-5** REGISTRY
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (+)-Carvedilol
CN R-(+)-Carvedilol
FS STEREOSEARCH
MF C24 H26 N2 O4
LC STN Files: BEILSTEIN*, CA, CAPLUS, DRUGPAT, DRUGUPDATES, IPA, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



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REFERENCE 1: 128:18344

REFERENCE 2: 127:229175

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REFERENCE 5: 125:184727

REFERENCE 6: 125:96309

REFERENCE 7: 124:325510

REFERENCE 8: 123:101931

REFERENCE 9: 122:218

REFERENCE 10: 121:195381

L11 ANSWER 4 OF 4 REGISTRY COPYRIGHT 1998 ACS
RN **72956-09-3** REGISTRY
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (.+-.)-Carvedilol

CN BM 14190
CN Carvedilol
CN Coreg
CN DQ 2466
CN SKF 105517
FS 3D CONCORD
DR **107741-96-8**
MF C24 H26 N2 O4
LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PNI, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL
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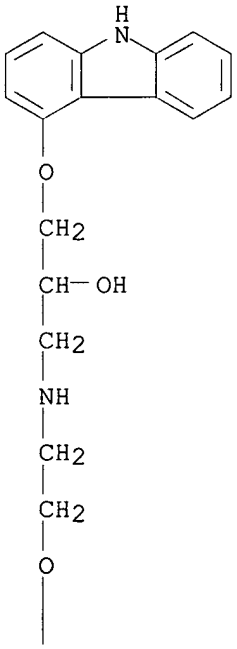
PAGE 1-A



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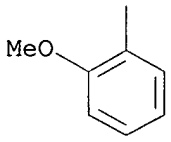

229 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
233 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:248603

REFERENCE 2: 128:248580

REFERENCE 3: 128:238868

REFERENCE 4: 128:238867

REFERENCE 5: 128:225946

REFERENCE 6: 128:212968

REFERENCE 7: 128:201064

REFERENCE 8: 128:196701

REFERENCE 9: 128:188316

REFERENCE 10: 128:158915

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FILE LAST UPDATED: 12 May 1998 (980512/ED)

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=> d l16 sta que nos

L2 STR
L4 211 SEA FILE=REGISTRY SSS FUL L2
L5 270 SEA FILE=HCAPLUS ABB=ON PLU=ON L4
L8 79 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 (L) (?CARD? OR HEART OR INFAR?)
L10 58 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND (?ANTAG? OR ?ADRENO? OR RECEP?)
L14 375 SEA FILE=HCAPLUS ABB=ON PLU=ON (ALPHA OR BETA)(2W) ADRENORECEPTOR(2W)ANTAGONIST?
L15 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 AND HEART(W)FAIL?
L16 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L15 NOT L10

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=> d l16 1-3 bib abs

L16 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 1998 ACS
AN 1998:240932 HCAPLUS
TI Comparative efficacy of a DA2/.alpha.2 agonist and a .beta.-blocker

in reducing adrenergic drive and cardiac fibrosis in an experimental model of left ventricular dysfunction after coronary artery occlusion

AU Latini, Roberto; Masson, Serge; Jeremic, Gordana; Luvara, Giuseppina; Fiordaliso, Fabio; Calvillo, Laura; Bernasconi, Roberto; Torri, Mauro; Rondelli, Ivano; Razzetti, Roberta; Bongrani, Stefano

CS Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche "Mario Negri,", Milan, Italy

SO J. Cardiovasc. Pharmacol. (1998), 31(4), 601-608
CODEN: JCPCDT; ISSN: 0160-2446

PB Lippincott-Raven Publishers

DT Journal

LA English

AB Attenuation of neuroendocrine activation may be beneficial in congestive **heart failure**. Sympathetic nervous system overactivity can be reduced by receptors blockade or by reducing norepinephrine (NE) spillover. This study evaluated and compared the effects of a DA2-dopaminergic receptor/.alpha.2-adrenoceptor agonist (CHF-1024) and a .**beta**.1-**adrenoreceptor antagonist** in terms of hemodynamics, ventricular remodeling, .beta.-adrenergic drive, and cardiac fibrosis after myocardial infarction (MI) in rats. MI was induced by left coronary artery ligation in 213 rats, whereas 12 were left unoperated on. After 2 mo, the operated-on animals were treated for 1 more month with CHF-1024 at either 0.33 mg/kg/day (low dose) or 1 mg/kg/day (high dose) or with metoprolol (10 mg/kg/day), delivered through implanted osmotic minipumps. Plasma concn. and urinary excretion of NE were measured before the rats were killed. Hemodynamic variables were measured and morphometric anal. was done on the diastole-arrested hearts to quantify left ventricular remodeling and interstitial collagen d. Metoprolol treatment tended to normalize LV end-diastolic pressure (LVEDP). CHF-1024 at either dose, and metoprolol, significantly reduced collagen deposition in LV of infarcted animals (from 8.8 .+-. 0.5% LV area in vehicle-treated rats to 6.6 .+-. 0.2% or 6.4 0.2% after the low or high dose of CHF-1024, resp.; $p < 0.05$). Similarly, CHF-1024 at either dose reduced the plasma concn. of NE (from 224 .+-. 53 pg/mL to 60 .+-. 7 pg/mL or 87 .+-. 13 pg/mL; $p < 0.05$) and urinary excretion of NE in rats with MI, whereas .beta.-blockade did not affect these variables. In conclusion, CHF-1024 infused for 1 mo to rats with LV dysfunction reduced heart rate, NE spillover, and collagen deposition, without unwanted effects, only appearing at the higher dose. Effective .beta.-blockade with metoprotol reduced LVEDP with no effects on heart function. Neither DA2/.alpha.2 stimulation nor .beta.-blockade altered LV remodeling after coronary artery ligation.

L16 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 1998 ACS

AN 1997:730698 HCAPLUS

DN 128:30219

TI Treatment of **heart failure** with left ventricular dilatation functional insufficiency by .**beta**.-**adrenoreceptor antagonist**

AU Gou, Yingjie

CS Dep. of Med., Railway Ministry 1st Eng. Bureau Central Hosp., Weinan, 714100, Peop. Rep. China

SO Shaanxi Yixue Zazhi (1996), 25(1), 17-19
CODEN: SYZAEL; ISSN: 1000-7377

PB Shaanxi Yixue Zazhi Bianji Weiyuanhui

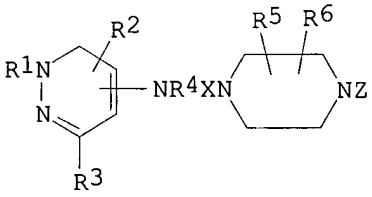
DT Journal

LA Chinese

AB 36 Patients with left ventricular dilation insufficiency **heart failure** refractory to conventional therapy received addnl. .beta.-blockader, propranolol. 2-3 Wks after the

addn. of propranolol, most of their heart function restored II grade, and chest film, ECG, ultrasonic all demonstrated marked improvement of left ventricular dilatation function. 2 Non responsive cases were related with hypokalemia and arrhythmia, and 1 deteriorated case was due to advanced end stage **heart failure**. The results suggest that the **heart failure** refractory to conventional therapy may try .beta.-blocker.

L16 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 1998 ACS
AN 1991:23972 HCAPLUS
DN 114:23972
TI Preparation of piperazinylalkyl-3(2H)-pyridazinones as cardiovascular agents
IN Blaschke, Heinz; Stroissnig, Heimo; Fellier, Harald; Enzenhofer, Rita
PA Lentia G.m.b.H. Chem. und Pharm. Erzeugnisse-Industriebedarf, Fed. Rep. Ger.
SO Ger. Offen., 26 pp.
CODEN: GWXXBX
PI DE 3902316 A1 900802
AI DE 89-3902316 890126
DT Patent
LA German
OS MARPAT 114:23972
GI



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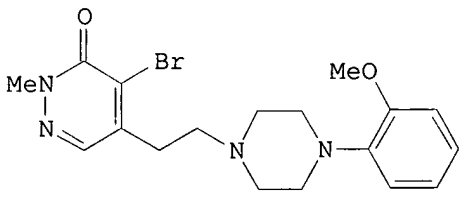

II

AB The title compds. [I; R1 = H, Ph, PhCH2 (substituted) alkyl; R2,R3 = H, halo, alkoxy, alkyl; R4 = H, alkyl, Ph, PhCH2, PhCH2CH2; R5, R6 = H, alkyl; X = (OH-, alkyl-, or amino-substituted) alkylene; Z = (substituted) Ph, naphthyl, pyridyl, thiazolyl], were prepd. Thus, a mixt. of 2-methyl-4,5-dibromo-3(2H)-pyridazinone, 1-(2-aminoethyl)-4-(2-methoxyphenyl)piperazine, and K2CO3 in DMF was stirred 20 h at 80.degree. to give a mixt. of title compd. II and its positional isomer. I bound to .alpha.1 adrenoceptors with Ki = 2.0-103.